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HEBERDEN ORATION

HEBERDEN'S NODES. A CLINICAL DESCRIPTION OF OSTEO-ARTHRITIS OF THE FINGER JOINTS*

BY

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It is indeed a great honour to be invited to deliver the Heberden Oration and to thus be linked with such medical scholars as have appeared in this role in the past. It is hoped that they will not feel uneasy at being forced thus to be associated so intimately with me! It is indeed a happy occasion to be invited to talk to the Heberden Society which includes among its membership so many close friends. It was my pleasure to be a dinner guest at a meeting of the Society in 1947, when Dr. Copeman was President.

Above all, it moves me deeply to have this opportunity to pay my respects to the man you have chosen as your patron, William Heberden, after whom your Society has been named. I, too, quite independently, chose him as my patron over 15 years ago when starting to study Heberden's nodes. My attempt to answer a simple question, which I thought might take several months, started me on a quest which is still continuing. My talk to-day is about what Heberden called *digitorum nodi*, which have come to be known throughout the world as Heberden's nodes. During his lifetime Heberden was a leading clinician, a successful practitioner, an author, and an essayist. He was the first to study and describe angina pectoris. His commentaries on disease, which were written in Latin, were translated into English and published posthumously. So far as I can find what he wrote amounted to 79 words in English about enlargement of the fingers (Heberden, 1803):

> What are those little hard knobs, about the size of a small pea, which are frequently seen upon the fingers, particularly a little below the top, near the joint? They have no connexion with the gout, being found in persons who never had it; they continue for life; and being hardly ever attended with pain, or disposed to become sores, are rather unsightly than inconvenient, though they must be some little hindrance to the free use of the fingers.

It is obvious that his words about *digitorum nodi* have set some kind of a record for effective brevity!

The really significant statement was that the nodes were certainly not due to gout. He did not say what they were, so I have more or less deliberately perverted the term to mean degenerative joint disease or osteo-arthritis of the finger joints.

Let me here acknowledge the assistance received in this work from my collaborators, each a specialist in his own field, without whose help this story would not have been possible. They include Dr. A. H. Hersh, Professor of Biology at Western Reserve University, whose advice, consultation, and statistical computation made the work on genetics possible, Dr. H. Hauser, for taking and interpreting the radiographs and collaborating on the question of radiological appearances, Dr. E. E. Beard, for collaborating on the study of the menopause, and Dr. L. J. Karnosh for help on the effect of nerve injury on Heberden's nodes. The help and friendship of these men have been precious for many years.

Incidence

My interest in this condition was aroused after seeing a man with well-developed enlargements of the fingers (Fig. 1, overleaf). He told me that he had four sisters with the same condition. The question arose whether or not this combination of disease was significant, or whether it might have affected five members of the same family by chance alone. The only way to settle this question was to discover

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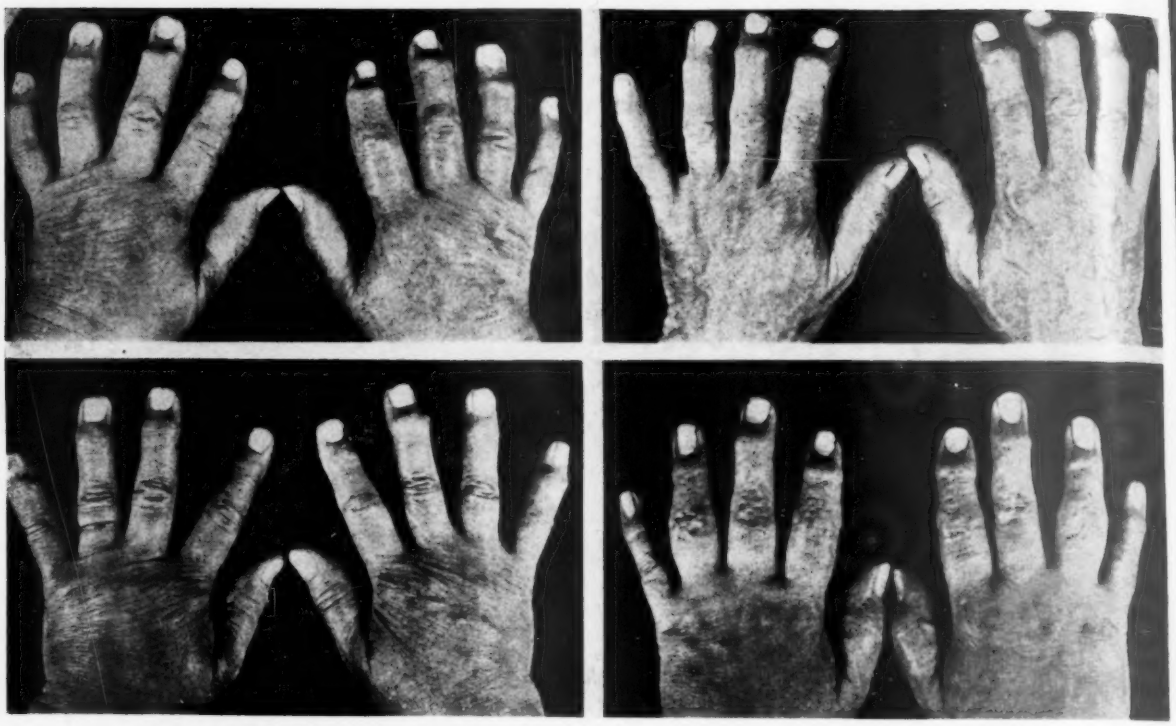

Fig. 1.—Hands of four living affected members of one family, showing well-marked Heberden's nodes.

the incidence of this disease in the population in general. Nearly 8,000 subjects were examined and the incidence determined for each sex and decade of age (Stecher, 1940).

This survey showed that enlargement of the terminal joints of the fingers arose in two different manners. Many men of all ages with one finger enlarged stated that this was the direct result of a single, painful injury. The commonest accident recorded was that of being hit on the end of the finger by a baseball. The finger became very painful, it swelled immediately, remained tender and sore for days to weeks, and became deformed, reaching a resting stage in several months. No further finger became involved, and it was concluded that this was a true traumatic arthritis to be designated traumatic Heberden's node. This deformity, once produced, lasted throughout the remainder of life, and was found in men of all ages, the incidence increasing with age. On the other hand, women related that one finger began to enlarge gradually in the late forties without known precipitating cause, other fingers became enlarged one after another until many or nearly all of the fingers were involved. The fingers were sensitive and tender during the period of development, but this phase passed after a few months. This condition was designated idiopathic Heberden's nodes.

Familial Involvement

When the incidence of Heberden's nodes had been determined for various sex and age groups it was easy to compute the probability of the disease occurring by chance alone in any family group (Stecher, 1941). In the family cited above, it was found to be one chance in ten million. In other large families, depending upon the numbers and age of the people involved, it was found to be one chance in five million and one chance in two hundred. The probability of seeing three families, constituted as has been described and occurring by chance alone, can be computed by multiplying ten million by five million by two hundred, so that it would have been necessary to examine every family on earth from the beginning of time to find the combination reported. It was apparent that some factor other than chance determined this phenomena, and heredity seemed the best explanation.

To test this hypothesis further family histories were obtained of the fingers of the mothers and sisters of 64 patients with Heberden's nodes. Most of the sisters, both affected and non-affected, were examined personally. When these women were sorted into age groups by decades and the incidence for each decade applied, idiopathic Heberden's nodes were found to occur twice as frequently in the mothers and three times as frequently in the sisters

of affected women as could be expected in the general population on the basis of chance alone. As a further check a control series was developed by examining the sisters of women at the City Hospital who had no joint disease. Heberden's nodes occurred about as frequently in these sisters as would be expected in the general population, and this further strengthened the conviction that idiopathic Heberden's nodes were determined by heredity.

Mode of Inheritance

An attempt was then made to determine the mode of inheritance of this condition (Stecher and Hersh, 1944). By this time pedigrees of 74 persons had been assembled and an analysis was made of these data. The affected propositi and their siblings included 127 men and 215 women. The difference in the number of men and women in the group is due to the fact that 72 of the 74 propositi were women. When these are subtracted from the total group there remains 125 men and 143 women, a fair approximation to the proportions of men and women in the general population of this age distribution.

Examination of the pedigrees showed at once that the incidence in women was high compared to that in men. For this reason each sex was considered separately in a genetic analysis. Considering first the women, it was found that 108 of the 215 women, or one half, were affected, the 1 : 1 ratio suggesting immediately that the character depends upon a single autosomal dominant gene. When this is the case one parent is invariably expected to be affected. Actually, mothers were recorded as affected in 25 of the 74 families. In two families the maternal grandmother was involved, but the mother, dying before the age of 35, had been spared. Only one father was recorded as affected, but this family added nothing to the genetic analysis because the mother was also affected and only one daughter, the propositus, resulted from the match. In four families in which the mother was unaffected, there was reason to believe that the character was transmitted through the unaffected father. In two of these instances, the paternal grandmother and in two other instances a paternal aunt had Heberden's nodes. In eleven families, including the two mentioned above, the mothers died before the age of 50, so might have been genetically affected without demonstrating the character. In four families the women were affected in three successive generations. Of the 74 families some antecedent involvement was discovered in 42 instances but was lacking in the 32 others.

Although Heberden's nodes may seem to be dominant in women the condition is certainly not so in men. Of the 127 males of this series only four were recorded as affected. Heberden's nodes may be recessive. Genetic examples are known of factors dominant in one sex and recessive in others. These include colour variation in cattle, the development of horns in sheep, and hereditary baldness in humans. Baldness is dominant in men and recessive in women. With a heterozygous constitution (*Aa*) men develop the trait and transmit baldness to one half of their offspring. Women with this constitution do not exhibit the condition but transmit it to one half of their children. Women become bald only when they are homozygous (*AA*). With Heberden's nodes the simplest modification is to assume that the condition is recessive in men. With matings of a heterozygous person with normal ($Aa \times aa$), one half of the children will be heterozygous (*Aa*). The women of this constitution will develop Heberden's nodes while the men will not. The men who have Heberden's nodes are homozygous (*AA*). According to this assumption an equal number of men and of women are of the heterozygous (*Aa*) constitution. Such men were assumed to have been the fathers in those families where no antecedent involvement was known. Furthermore, for a man to be affected, both parents must transmit the character to him, though only the mother is likely to show it.

Gene Frequency Analysis

The above hypothesis was tested by gene frequency analysis. For the subsequent discussion *D* was used to represent the dominant gene for Heberden's nodes and *d* the recessive normal allele. In the former study the highest incidence in white women over 70 years of age was found to be about 30 per cent. If this is accepted as complete penetrance we may assume that 70 per cent. of women are homozygous recessives and are *dd* in constitution or completely normal so far as Heberden's nodes are concerned (Table I).

TABLE I

GENE FREQUENCY CALCULATION OF HEBERDEN'S NODES

$D^2 + 2DR + R^2 = 1$

Persons		Genes	
D^2	= 0·027		
$2DR$	= 0·272	D	= 0·163
R^2	= 0·700	R	= 0·837
Total	0·999		1·000

The proportion of the 30 per cent. who are

DD and *Dd* in constitution may be readily calculated from the well-known formula for gene frequency analysis in a population in genetic equilibrium mating at random. According to the formula, homozygous dominants *DD*, heterozygous *Dd*, and homozygous recessives *dd*, are present in the population in the relative numbers Q^2, $2PQ$, and P^2 respectively, where $P + Q = 1$.

Since $P^2 = 0{\cdot}70$, $P = 0{\cdot}837$, from which Q is readily known from the relations $P + Q = 1$. The values of $2PQ$ and Q^2 are also easily calculated. The result shows that individuals with the constitutions *DD*, *Dd*, and *dd* are present in the population in the relative proportions of 0·027, 0·272, and 0·70 respectively. According to this hypothesis males of the constitution *Dd* are phenotypically normal. Only 2·7 per cent. of males have a genetic constitution which would cause the trait to develop.

Types of Matings

Since the proportion of the various constitutions for Heberden's nodes are known, the types of matings which can be expected to occur at random can be predicted (Table II). The top figure gives the proportion of each type of mating expected in the general population. The figure in brackets gives the actual number of each type of mating expected in this group of 74 families. Since each pedigree was discovered through an affected child and never from a parent, no mating of type *dd* × *dd* is included.

TABLE II

TYPES OF MATING FOR HEBERDEN'S NODES

No. in brackets = Actual No. Expected

Constitution of Fathers	Constitution of Mothers		
	DD $q^2 = 0{\cdot}027$	*Dd* $2pq = 0{\cdot}272$	*dd* $p^2 = 0{\cdot}70$
DD $q^2 = 0{\cdot}027$	0·00073 (0·1)	0·0073 (1·1)	0·0189 (2·8)
Dd $2pq = 0{\cdot}272$	0·0073 (1·1)	0·074 (10·8)	0·1904 (28·0)
dd $p^2 = 0{\cdot}70$	0·0189 (2·8)	0·1904 (28·0)	0·490 (None)

Although is was not possible to recognize the different genotypes with certainty in all families, an attempted rough classification was justified. A total of 44 families with inheritance from the mother were expected. Of these 29 were identified with a fair degree of certainty; these include 25 families with the mother affected, two families with maternal grandmother affected, and two additional families with affected sons. If ten other families, omitted from the above classification because the mother died so young that her constitution could not be recognized, are considered as having heterozygous mothers, this group becomes 39 compared to 44 expected theoretically. Assuming random mating, twelve heterozygous fathers are expected in this group of 44 families leading to double inheritance, and a 3 : 1 ratio of expected affected. Of the 29 families identified, therefore, we expect an appreciably greater frequency than the straight 1 : 1 ratio. According to the table of matings 28 families are expected with no parents showing the trait. Although 30·8 are expected without inheritance from the mother, 35 families are found. In these families it is concluded that inheritance is through the father and the rate 1 : 1 is expected.

Correction for Small Family Size

The above ratios are theoretical and cannot be realized in human material such as is dealt with here. Corrections can be made for small family size and for lack of penetrance. The desirability of the first is obvious. Although one half of the children of affected families are expected to be affected, this ideal is upset by the vagaries of chance. Some families will have one half of the children affected, some may have all the children affected, and some may have none affected; and every possible combination may be met with. Such variations as these array themselves according to the quadratic equation. If one starts only with affected individuals and studies their siblings, as we have done here, those families without affected children will not be included and the results will exceed the usual Mendelian ratios. It is therefore necessary to correct for small family size. The corrections are made according to the method of Hogben. Table III shows 29 families with maternal inheritance. Of 95 daughters, 57 are observed affected compared with 55·446 expected affected.

TABLE III

HEBERDEN'S NODES

SISTERS AFFECTED/EXPECTED AFFECTED

(Correction for small family size—Mother affected)

Family Size	No. of Families	Sisters		Ratio	
		Total	Affected	Factor	Expected
1	5	5	5	1·0	5·0
2	8	16	10	1·333	10·664
3	3	9	6	1·714	5·142
4	5	20	8	2·133	10·665
5	5	25	11	2·581	12·905
6	2	12	10	3·048	6·096
8	1	8	7	4·016	4·016
Total ..	29	95	57		54·488
Percentage			60		57·2

Table IV shows 35 families without maternal inheritance. Of 96 daughters, 48 are found affected compared with 57·64 expected. A higher proportion of affected are found in the group with suspected double inheritance than in that with single inheritance.

TABLE IV

HEBERDEN'S NODES
SISTERS AFFECTED/EXPECTED AFFECTED
(Correction for small family size—No parent affected)

Family Size	No. of Families	Sisters		Ratio	
		Total	Affected	Factor	Expected
1	10	10	10	1·0	10·0
2	3	6	3	1·333	4·0
3	11	33	14	1·714	18·854
4	8	32	15	2·133	17·064
5	3	15	6	2·581	7·743
Total ..	35	96	48		57·661
Percentage			50		60

Paternal Inheritance

Attempts were made to correct for incomplete penetrance because of lack of age, but the details are not presented. They were very crude and gave results which were much too high. Instead, an effort was made to contact these subjects again and in the course of 12 years, two women formerly negative in the group with uninvolved mothers and four women in the group with mothers involved developed Heberden's nodes. This brought the percentage affected to 50 per cent. in the first group and 60 per cent. in the second group. It was assumed that in families without affected parents the trait was transmitted by a heterozygous father, and 50 per cent. affected was to be expected among the daughters. The affected mothers mating at random had a 30 per cent. chance of having heterozygous husbands (Table V).

TABLE V

FAMILIES WITH HEBERDEN'S NODES

Types of Matings		Affected	Normal
(1) Normal mother + Carrier father	1 : 1	50	50
(2) Affected mother + Normal father	1 : 1	50	50
(3) Affected mother + Carrier father	3 : 1	75	25

AFFECTED MOTHER WITH RANDOM MATINGS IN 100 FAMILIES (per cent.)

Type	No. of Matings		Affected	Normal
2	70	1 : 1	35	35
3	30	3 : 1	22·5	7·5
Total ..	100		57·5	42·5

In 70 per cent. of the normal families, 50 per cent. of the daughters, and in 30 per cent. of the families with heterozygous fathers 75 per cent. of the daughters, are expected affected. In the combined group 57·5 per cent. are expected affected.

Double Inheritance

In twelve families with known double inheritance because of the appearance of affected sons, we expected a 3 : 1 ratio of affected daughters. These families had 33 sons and 29 daughters. Of the sons fourteen out of 33 were found to be affected, very close to a 1 : 1 ratio. Only 1 : 3 is expected here, but the result is biased because of the small number of sons and the fact that the families were chosen because of an affected son. Twenty of 29 women were found affected. This is 20 : 9 or 2·2 : 1, somewhat lower than the theoretical expectancy but much higher than the usual 1 : 1. Two of the above sibships were used in a subsequent study of a large family of three generations in which expressivity was discussed at length. Two women who theoretically and genetically should have had Heberden's nodes are listed as normal. They do show small concretions of calcium in the tendonous attachments of the extensor tendons which may qualify them as genetically affected. If two normals of these nine are transferred to the twenty previously accepted positive cases, it would show 22 affected against seven normals, slightly over the 3 : 1 theoretical expectancy.

Therefore it is our concerted opinion that idiopathic Heberden's nodes depend upon a single autosomal gene sex influenced to be dominant in females and recessive in males. The gene frequency in the general population is 0·163, and three constitutions are recognized in the population:

DD, homozygous affected 0·027, the incidence in men,

Dd or heterozygous constitution 0·272, the sum of these constitutions 0·027 + 0·27 = 0·297 or 0·30 give the incidence in women and *dd* 0·70 which is homozygous normal. Homozygous affected women have not been identified.

Association with Other Forms of Arthritis

A survey was undertaken to determine the frequency of osteo-arthritis of the various joints of the hand (Stecher, 1950). The results are shown in Fig. 2 (overleaf). It is obvious that both hands are about equally involved. In the order of decreasing frequency, it is seen that involvement affects the

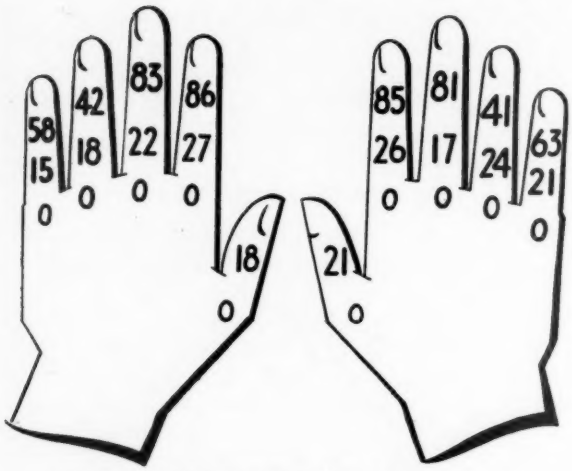

Fig. 2.—Distribution of arthritis in 100 pairs of hands.

terminal joints of the index finger, the middle finger, the little finger, and the ring-finger. The proximal joints of the four fingers are involved in about one-fourth of the cases and there is a substantial increase of involvement in the proximal joints of the right hand over the left hand. It is seen that the distal joint of the thumb is involved as frequently as other proximal joints. The metacarpophalangeal joints have never shown involvement in our observations. This experience has made it reasonable to diagnose osteo-arthritis of the proximal joints of the fingers, whereas before rheumatoid arthritis seemed the only proper diagnosis.

The association of Heberden's nodes with osteo-arthritis of other joints of the body was then considered (Stecher, 1946a). Heberden's nodes in the past have been considered as "The commonest manifestation of degenerative joint diseases" and as "diagnostic of degenerative joint disease". Such general statements have not been confirmed in our studies. In a series of 94 women with Heberden's nodes, twelve (12·6 per cent.) were found to have other osteo-arthritis. In eleven patients this involved one knee, in one patient it involved one hip. It was never severe enough to incapacitate the patient, but it did cause inconvenience and discomfort in most instances. Deformity was not marked. Limitation of motion and crepitus was noted in all the affected knees. Several patients had a decided limp and required a cane or crutch. All took acetylsalicylic acid and many had resorted to physical therapy, diathermy, or massage. Apart from the twelve patients just mentioned, nineteen complained of arthritis or rheumatism. They had transient stiffness, occasional soreness, and questionable swelling, and resorted to acetylsalicylic acid for relief. These symptoms were troublesome but they were not objective signs of disease warranting a clinical diagnosis of degenerative joint disease. All knees were tested by palpation during motion for crepitus. Crepitus was noted in 35 (36 per cent.) of the cases. This condition was often unnoticed by the patient. It cannot be considered normal, but it does not of itself warrant a diagnosis of degenerative joint disease, and is not necessarily a forerunner of future joint disability. The significance of crepitus in these cases is not clear. Of 109 patients of the control series, three had definite degenerative joint disease of the knee, diagnosed because of pain, limitation of motion, and deformity, and comparable to that of the persons mentioned in the first group. No instance of other arthritis and rheumatism except ankylosis of one knee due to tuberculosis without objective signs were discovered in this series. Crepitus was noted in only 25 or 23 per cent. of the subjects.

The differences revealed between the two series are more apparent than real. The patients with Heberden's nodes were examined many times over a long period. There was thus frequent opportunity to complain of rheumatism or of arthritis or to discover crepitus. The members of the control series were seen but once and since they had not been thinking about arthritic complaints it seems certain that many details were overlooked. The fact remains that 94 patients with Heberden's nodes showed relatively little crippling generalized degenerative joint disease. I do not believe that Heberden's nodes are a part of a generalized osteo-arthritic syndrome.

Heberden's Nodes and the Menopause

A definite association was established between the development of Heberden's nodes and the menopause (Stecher and others, 1949). This was found in a series of 99 women in whom the age at onset of Heberden's nodes was compared with age at the menopause. These events occurred within one year of each other in ten instances and within 3 years of each other in one half of the cases. In individual patients Heberden's nodes appeared at times ranging from 20 years before to 15 years after the menopause. The coefficient of correlation was found to be + 0·46, indicating odds of less than 1 : 1,000,000 that such a correlation would occur by chance alone. Even this high degree of correlation does not prove that the climacteric is a cause of Heberden's nodes. The average age at the menopause was 46·2 years in the fifty women in whom

the earliest onset of Heberden's nodes was at 33 to 49 years. The average age at the menopause was 50·5 years (4·3 years later) in the 49 women in whom the onset of Heberden's nodes occurred later, from 50 to 65 years. It is most likely that these events have aetiological factors in common. Both must be considered as manifestations of the ageing process. Since Heberden's nodes occur only in people who are genotypically susceptible, the climacteric has to be considered as a contributory though important factor in their production.

Importance of Nerve Supply

Heberden's nodes apparently fail to develop in the absence of a normal and intact nerve supply to the fingers or hands. They have failed to develop in the presence of peripheral nerve damage, spinal cord disease, or palsies of cerebral origin. Stecher and Karnosh (1947) described a woman with a median nerve injury of the right hand who later developed Heberden's nodes in all fingers except those supplied by the injured nerve, the left second, third and fourth fingers. In a second case, a woman with weakness and partial lack of development of the right hand due to former anterior poliomyelitis had marked Heberden's nodes on the unimpaired left hand only (Fig. 3).

Fig. 3.—Hands of a woman with Heberden's nodes in the left hand only, the right having been affected by anterior poliomyelitis.

Similar cases have been seen and described by Hench (1947) and Beard (1947). Heberden's nodes also failed to develop in hands paralysed by cerebral accidents, although present on the normal side in cases described by Coste and Forestier (1935). Trophic disturbances after identifiable injury to the central nervous system lead to increased circulation to the limb, demineralization of the bones, and protection against the development of Heberden's nodes. A total of three such cases from our own experience and nine from the literature may be cited.

The literature about Heberden's nodes is not profuse but two studies recently reported (Peltola and Ahto, 1953; Roversi and Mars, 1954) are interesting. These workers found cervical arthritis in patients with Heberden's nodes and attributed the nodes to pressure or irritation of the nerves by exostoses emerging from the spinal canal. What the mechanism of such an influence may be is obscure. This hypothesis is at complete variance with our own observations and conclusions. Clinically, no trophic disturbance of skin or finger tissues nor alteration in normal circulatory control have been described in Heberden's nodes, but the few cases examined since these publications came to our attention have revealed exostoses, decreased width of intervertebral disks, and bone condensation in the cervical region.

Other Clinical Features

Blood Pressure.—To determine whether the condition was associated with high blood pressure (Stecher and Hauser, 1948), a comparison was made between 112 women with Heberden's nodes and 92 women of approximately the same age distribution, but otherwise selected at random. It was found that average blood pressure for each age group by decades was the same. After combining the series into one group no significant association between Heberden's nodes and hypertension could be demonstrated. In a series of 82 women with hypertension, Heberden's nodes were not found more frequently than could be expected from their incidence in the population in general. It was concluded that the relation of Heberden's nodes to hypertension does not differ from that of degenerative disease of other joints.

Obesity.—Although a strong positive association has been demonstrated between degenerative joint disease and obesity, no such association was found in this series; in this respect there is a wide difference between Heberden's nodes and other degenerative joint disease.

Roentgenological Appearance.—A detailed study was made of the clinical and roentgenological appearances of osteo-arthritis of the finger joint (Stecher and Hauser, 1948). In the original survey

Heberden's nodes were defined as enlargements of the terminal joints sufficient to be seen and felt as a definite bony ridge across the palmar and the dorsal surface of the last joint. The shape and size of this enlargement varied considerably. At times "two small nodules" were identified, but more often the enlargement consisted of a solid bony ridge. As the disease advanced a flexion deformity causes the end phalanx to bend inwards, and the final degree of involvement shows a lateral deviation from the straight line.

It soon became apparent that osteo-arthritis of the fingers was not confined to the terminal joints alone. In many cases the proximal joints were involved. As experience accumulated it became possible to diagnose osteo-arthritis of the finger joints with only the proximal joints involved. This condition accompanied general good health, lack of involvement of other joints, and middle age in women patients.

Conventional radiographs of the fingers as shown in posterior-anterior views of the hand were disappointing, but the lateral view invariably showed bone changes, in the form of spurs arising first from the proximal, dorsal aspect of the distal phalanx, the palmar surface of the proximal aspect of the distal phalanx, and the distal aspect of both dorsal and palmar surfaces of the distal end of the middle phalanges. These spurs varied in size and shape, the joint spaces being often uneven, and the surfaces unequal, and roughened. Demineralization of bone was never seen, and usually the joint surfaces showed increased mineralization.

Some patients who had had well-marked Heberden's nodes for 20 years showed no involvement of the proximal joints. Other patients showed involvement, beginning perhaps in the proximal joint, until most of the joints of the hand become involved. Changes in the proximal joints, which were usually obvious both in the postero-anterior and lateral views, consisted of a broadening in both diameters of the proximal end of the middle phalanx sometimes with overlapping of the distal end of the proximal phalanx. True spur formation of the proximal end of the middle phalanx was rarely seen, but it did occur from the distal end of the proximal phalanx. The joint spaces were markedly decreased and the bone characterized by condensation rather than rarefaction.

Trauma.—Heberden's nodes may be caused by injury (Stecher and Hauser, 1954); they reach a high incidence in men in the third decade of life. If trauma has been the cause the patient invariably remembers the incident and describes it vividly; the enlargement occurs promptly and the condition remains stationary thereafter. The radiographic appearances are differentiated, in that the most marked enlargement is seen in the dorsal spur arising from the proximal end of the distal phalanx. This is usually large and broad and has its beginning some distance away from the proximal end of the joint. The tip of the spur is broad and rounded, and the joint space usually unaltered.

Study of a Large Family

An opportunity to test some of these theories was offered by a large family with a high incidence of Heberden's nodes (Stecher and others, 1953), which offered data on thirty individuals in three generations, including nine affected individuals (Fig. 4).

Three sisters were involved in the first generation. The first sister had an involved daughter and three

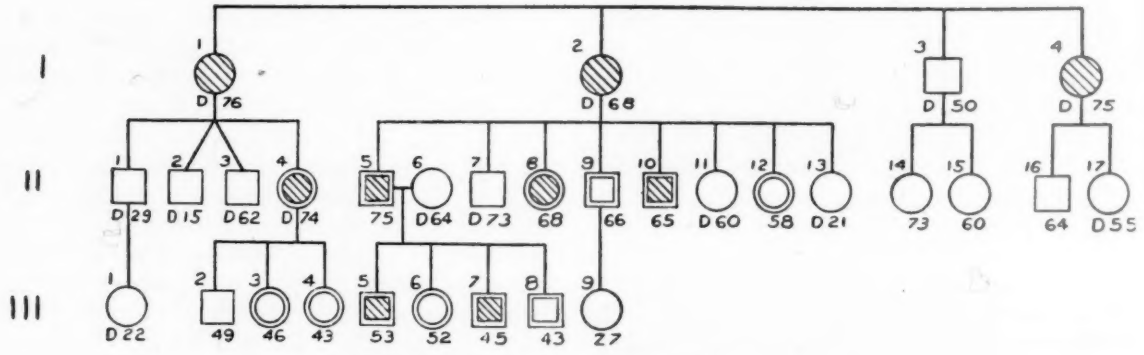

FIG. 4. Pedigree showing involvement in three generations.
Shaded individuals have idiopathic Heberden's nodes.
Symbol with double outline indicates that the individual was examined.
II-9 and III-8 have traumatic nodes.
II-12 shows islands of bone, which probably represent poor expressivity of idiopathic Heberden's nodes.

normal sons. The second sister mothered eight children, of which two brothers and one sister are involved. The first of this second sister's sons fathered four children; of three sons, two were involved, and the one daughter was rated negative. The third sister had a son and a daughter, both of whom are reported normal.

Two men at least (II-9 and III-8) had traumatic Heberden's nodes only, and one man with marked idiopathic Heberden's nodes showed changes in the right middle finger consistent with traumatic Heberden's nodes. In as much as this finger enlarged years before the other and he did suffer an injury it seems that a diagnosis of traumatic nodes is justifiable. The sibship of eight children included four men and four women; of the four men, two, or one half, show idiopathic Heberden's nodes, and of the four women, only one showed idiopathic Heberden's nodes, whereas we should expect three of the four to be affected. One sister died at age 21 and must be ignored, but one died at 60 and was rated negative; we must accept this at its face value because these people were alert to the condition. One woman (II-12) aged 58 showed absolutely no clinical suggestion of Heberden's nodes, but lateral *x*-ray pictures showed small islands of bony spurs arising from the dorsal aspect of the proximal end of the distal phalanges, and though she was rated as negative, these findings are possible minor manifestations of Heberden's nodes.

If our theory is correct, the mother, II-6, of the family of four in the third generation, must have been involved. She is listed as normal, but according to the theory she must have had the constitution for Heberden's nodes; she had either not developed them when she died age 64, or they were so poorly expressed that they were not recognized.

The woman represented in III-6 must eventually develop Heberden's nodes, but when last seen at the age of 52, she showed no suggestion of the condition (radiographs were not taken).

This large kindred supports the theory of a single genetic sex-influenced factor, usually, but not always, dominant in women and recessive in men. The exceptions can be accounted for by lack of penetrance or poor expressivity.

Conclusions

Idiopathic Heberden's nodes may occur without clinical evidence of other osteo-arthritis. Involvements of knees, hips, and spine do occur, but no more frequently than in any group of women of comparable age. It is inevitable that osteo-arthritis should involve other joints in some patients with Heberden's nodes, but this association is without aetiological foundation. My accumulated experience of osteo-arthritis of the finger joints, hips, and spine strongly suggests that three separate diseases have been confused by giving them the same name. This opinion will be supported if further study is made of osteo-arthritis in different joints, and obvious differences in age at onset, sex ratio, menopause, heredity, injury, and developmental anomalies are found. The fact that the histological picture of these diseases seems to be similar should not be allowed to mislead us.

This is one type of osteo-arthritis in which even the books suggest that therapy is ineffective. It is my policy to tell patients that they have a hereditary disease which comes at the time of the menopause. Since they have chosen their parents ill-advisedly in this respect and since their menopause cannot be prevented, there is little likelihood of preventing their disease. If the chemical and endocrinological changes which take place at the time of the menopause were understood, it might be possible to prevent or counteract them and delay the development of Heberden's nodes. Since the population is increasing in age and a higher proportion of elderly people survive, the incidence of this disease in the general population is likely to increase. During the period of development the affected fingers are sensitive and may be painful. This pain can be minimized by the use of aspirin. Some doctors recommend paraffin baths, but the patients to whom this has been suggested have stated that the pain is so slight and the treatment is so troublesome that they prefer to do without it. Many physicians are injecting hydrocortone into the terminal joints with happy results. I have not undertaken this personally and have no evidence that it is any more effective than the wearing of a copper bracelet on the wrist or carrying a horse chestnut in the pocket. For most patients the appearance of Heberden's nodes causes distress because of the cosmetic effect and because of fear that the nodes indicate the development of a crippling disease. Such is not the case, and the physician should reassure his patients on this point.

It may seem strange to spend so much time on such a little problem. It takes considerable courage to specialize in arthritis of the finger joints, but these studies were undertaken because it seemed that Heberden's nodes presented a clear-cut, simple disease, which lent itself to easy diagnosis, and offered the opportunity for clinical and statistical investigation. It was thought that information about this type of osteo-arthritis might be applicable to other forms, but such has not been the case. Our studies of Heberden's nodes will have been

justified if they serve as a stepping stone to better understanding of the more serious forms of joint disease.

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Nodosités d'Heberden. Description clinique de l'ostéoarthrite des articulations des doigts

RÉSUMÉ

Les nodosités d'Heberden peuvent exister sans que l'ostéoarthrite se manifeste ailleurs. L'atteinte concomitante des genoux, des hanches ou de la colonne vertébrale peut bien se voir, mais pas plus souvent que chez d'autres femmes d'un âge correspondant. Chez quelques malades ayant des nodosités d'Heberden l'ostéoarthrite est censée de frapper d'autres articulations mais cela n'implique pas un lien étiologique. Mon ample expérience d'ostéoarthrite digitale, coxo-fémorale et vertébrale indique nettement qu'on tend à confondre trois maladies différentes après leur avoir donné un seul nom. On trouvera des preuves à l'appui de cette opinion dans l'étude plus approfondie de l'ostéoarthrite de diverses articulations et en observant les différences nettes dans l'âge de début, rapport des sexes, ménopause, hérédité, traumatisme et anomalies évolutives. Le fait que les tableaux histologiques de ces maladies se ressemblent ne devrait pas nous induire en erreur.

Il s'agit ici d'un type d'ostéoarthrite dont le traitement est si futile que même les manuels l'admettent. Je dis toujours à mes clientes que c'est une maladie héréditaire apparaissant à l'époque de la ménopause et comme, de ce point de vue, leur choix de parents n'a pas été trop heureux et leur ménopause est inévitable, il est peu probable que l'on puisse empêcher la maladie. Si l'on comprenait les changements chimiques et endocriniens à l'époque de la ménopause, on pourrait peut-être les prevenir ou combattre et retarder ainsi l'apparition des nodosités d'Heberden. En raison de l'augmentation de l'âge moyen de la population générale due à la survie d'un nombre plus grand des personnes âgées, la fréquence de cette maladie tendra à augmenter. A la période évolutive les doigts atteints sont sensibles et souvent endoloris. On peut atténuer la douleur grâce à l'aspirine. Certains médecins recommandent des bains de paraffine, mais les malades à qui on les propose répondent que leur douleur est si faible et le traitement si incommode qu'ils peuvent bien s'en passer. Beaucoup de médecins injectent de l'hydrocortisone dans les articulations terminales avec heureux résultats. Personnellement, je ne l'ai jamais fait et je n'ai pas de raisons de croire que ce soit plus efficace qu'un bracelet en cuivre au poignet ou un marron d'Inde dans la poche. Les nodosités d'Heberden inquiètent les malades parce qu'elles enlaidissent et parce qu'elles représentent la menace d'une maladie mutilante. Il n'en est pas ainsi et le médecin doit les rassurer.

Nudosidades de Heberden. Descripción clínica de osteoartritis de las articulaciones digitales

SUMARIO

Las nudosidades de Heberden pueden existir sin osteoartritis en otras partes del cuerpo. El compromiso de la rodillas, caderas o de la columna vertebral se puede observar, pero no es más frecuente que en otras mujeres de edad correspondiente. En algunos enfermos con nudosidades de Heberden la osteoartritis atacará inevitablemente otras articulaciones, pero esto no basta para establecer una relación etiológica. Mi experiencia acumulada de osteoartritis digital, coxo-femoral y vertebral sugiere fuertemente una confusión de tres enfermedades diferentes que han recibido un solo nombre. Esta opinión recibirá apoyo del estudio ulterior de la osteoartritis de varias articulaciones con observar las obvias diferencias respecto a la edad de comienzo, proporción en los sexos, menopausia, herencia, trauma y anomalias evolutivas. El hecho de que los cuadros histológicos de estas enfermedades se parecen no debería inducirnos a error.

Se trata aquí de un tipo de osteoartritis que hasta los manuales reconocen la vanidad de tratarla. Suelo decir á mis pacientes que sufren de una enfermedad hereditaria que aparece durante la menopausia y como, en este respecto, no escogieron sus parientes muy juiciosamente y no pueden evitar la menopausia, tampoco se puede impedir la enfermedad. Si se comprendiera los cambios químicos y endocrinológicos durante la menopausia, quizás se podría prevenir o combatirlos y retrasar así la aparición de las nudosidades de Heberden. Al aumentar le edad media de la población general con la sobreviviencia de un número mayor de las personas de edad avanzada, se anticipa la más frecuente ocurrencia de esta enfermedad. En el período evolutivo los dedos comprometidos son sensibles y dolorosos. Se puede atenuar este dolor con aspirina. Ciertos médicos aconsejan baños de parafina, pero los enfermos a quienes se propone este remedio contestan que su dolor es de poca intensidad y el tratamiento poco cómodo de modo que prefieren se pasar sin él. Muchos médicos inyectan hidrocortisona con resultados afortunados. Personalmente nunca lo he hecho y no tengo razones para creer que ésta sea más eficaz que una pulsera de cobre en la muñeca o una castaña de Indias en el bolsillo. Las nudosidades de Heberden molestan por razones cosméticas y por el temor de una enfermedad mutiladora. No es así en realidad y el médico debe tranquilizar al enfermo.

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CARDIAC CHANGES IN RHEUMATOID ARTHRITIS

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The present investigation represents a continuation of inquiries by Jonsson, Berglund, Göhle, Ejrup, and Friedman (1952) first reported in 1949 at the Seventh International Congress of Rheumatology, New York.

Previous Investigations

Pathological Studies.—In a series of 25 autopsies of cases of rheumatoid arthritis, Baggenstoss and Rosenberg (1941) found "lesions of the type produced by rheumatic fever" in fourteen, though there was a history of rheumatic fever in only two; they concluded that "chronic infectious arthritis" and rheumatic fever might be in some way related. Fingerman and Andrus (1943) reported positive findings in nineteen of 61 cases, only two of which had a history of rheumatic fever. Reports have also been made by Bayles (1943), Bennett (1943), Young and Schwedel (1944), Rosenberg and others (1944), Clark and Bauer (1948), Graef and others (1949), Snorrason (1950), Bywaters (1950), and Sokoloff (1953). The percentages of rheumatic cardiac changes recorded by these authors varies a great deal, but 117 (27 per cent.) of the total of 439 cases assembled from these reports, revealed signs of rheumatic cardiac disease, and 133 (30 per cent.) signs of pericardial changes. Table I shows the nature of cardiac lesions in 288 of the cases reported in the literature, but in some reports the data were too incomplete for classification.

Clinical Studies.—In the majority of clinical investigations cardiac lesions were found much less frequently than in the pathological studies.

However, Kahlmeter (1934) found electrocardiographic changes in up to 27 per cent. of cases of "secondary chronic polyarthritis", and in up to 12 per cent. of cases of "primary chronic poly-arthritis"; in a control series, pathological electrocardiograms were obtained in only 2·6 per cent.

Dawson and Tyson (1936) found cardiac changes of a rheumatic nature in 7 per cent. of 100 cases. Monroe (1939) noted rheumatic valvular defects in 4 per cent. of 267 patients. Feiring (1945) reported pathological cardiac findings in 29 per cent. of 27 cases, but these included two with a history of rheumatic fever and another two in which that diagnosis seemed probable. Rogen (1947) reported positive cardiac findings in only 3 per cent. of 33 cases. Jonsson and others (1952) examined (by radiography, electrocardiography, hypoxaemia test, auscultation, and phonocardiography) 37 cases of rheumatoid arthritis and 37 controls; positive cardiac findings amounted to eleven cases (30 per cent.) in the rheumatoid group, and three (8·1 per cent.) in the control group.

Gil (1949) recorded endomyocardiac lesions in 5·5 per cent. of 360 cases; apart from a greater frequency of aortic defects, the symptoms were of the same type as those seen in rheumatic fever, and 3·3 per cent. showed

TABLE I

LOCALIZATION OF PATHO-ANATOMICAL CARDIAC CHANGES IN 288 CASES OF RHEUMATOID ARTHRITIS

Author	Date	Number of Cases	Cardiac Lesions			
			Rheumatoid Cardiac Changes	Valvular Changes	Myocardial and Vascular Changes	Pericarditis
Baggenstoss and Rosenberg ..	1941	25	14	11	12	5
Fingerman and Andrus ..	1943	61	19	19	2	7
Bayles	1943	23	6	6	3	4
Young and Schwedel	1944	38	25	24	4	19
Rosenberg and others	1944	30	16*	13	9	5
Clark and Bauer	1948	45	1	?	?	20
Graef and others	1949	66	26	24	7?	33

* Data regarding the exact nature of the rheumatic cardiac changes are lacking in two of these cases.

Clinical Data						
Case No.	Sex	Age (yrs)	Duration of Disease (yrs)	Heart Symptoms	Other Disease	Cause of Death
1	M	58	24	0	Encephalomalacia Bronchopneumonia	
2	F	65	13	0	Chronic nephritis	Uraemia
3	F	52	14	0	Empyema Bronchopneumonia Bronchiectasia	
4	M	52	1	Hypertension Acute pericarditis	Tubercular pulmonary induration Emphysema	Acute pericarditis
5	M	71	1	0	Myeloid leukaemia	
6	F	68	55	0	Subacute nephritis Septicaemia (?)	
7	M	80	5	Hypertension Cardionephrosclerosis	Ca. ventriculi + Diabetes mellitus	
8	F	60	25	Earlier pericarditis Suspected myocardial infarction	Bronchopneumonia Pleurit. chr. bilat.	
9	F	55	9	Hypertension E.C.G.: P. pulmonale	Bronchiectasiae Emphysema	Cardiac insufficiency (cor pulmonale)
10	F	64	7	Hypertension E.C.G.: Myocardial damage	Nephrosclerosis	Encephalomalacia
11	F	72	17	0	Bronchopneumoniae	
12	M	56	24	0	Myeloid leukaemia Nephrosis	
13	F	66	10	Hypertension E.C.G.: Cardiosclerosis	Arteriosclerosis Shrivelled kidneys	Cardiosclerosis

* In all positive cases (marked with +) only slight fibrosis.

electrocardiographic changes suggestive of myocardiac lesions. Rosenberg (1949) found pathological cardiac symptoms in 3·4 per cent. of 150 cases as against 2 per cent. in a control series. Bradfield and Hejtmancik (1950) noticed electrocardiographic and radiographic abnormalities in sixteen (35·8 per cent.) of 45 cases, but in not more than seven cases were the symptoms pronounced enough to justify a diagnosis of cardiac disease. Rosenberg, Bishop, Weintraub, and Hench (1950), in a clinical investigation of 114 cases of rheumatoid arthritis, 33 cases of ankylosing spondylitis, and a control group of 100 cases of the same age distribution, concluded that cardiac changes were not more frequent in the rheumatoid patients than in the control group. Lucchesi, Lucchesi, and Kneece de Melo (1947) found no sign of cardiac change in fifty patients with rheumatoid arthritis. Rohlin and Sundelin (1952), in 700 cases of rheumatoid arthritis, found, among 500 patients who had neither rheumatic fever nor hypertension, 2 per cent. with pathological lesions and 3·2 per cent. with suspected cardiac involvement; they did not think these percentages exceeded what might be expected in normal subjects.

Sury (1952) found "unquestionable cardiac disease" in 7 per cent. of 109 children; this was rheumatic in four patients (three with mitral stenosis and one with recurrence of acute carditis). Cobb, Anderson, and Bauer (1953) reported that 7 per cent. of deaths among 130 cases of rheumatoid arthritis were caused by valvular heart disease.

Material of Present Survey

Pathological.—A complete *post-mortem* examination of the heart was carried out in thirteen cases of typical rheumatoid arthritis, none of which had had rheumatic fever. After a macroscopic routine examination of the heart, specimens for a microscopic examination were obtained as follows:

(1) T-shaped block through the anterior wall of the heart, through the right and left ventricle and the septum.
(2) Longitudinal block through the aortic ring and the septum ventriculorum cordis, the septum membranaceum cordis, and downwards.
(3) Block from the posterior wall of the left ventricle on a level with the posterior papillary muscle.
(4) Block from the right ventricular wall midway between the coronary sulcus and the apex.
(5) Longitudinal block through the left anterior papillary muscle.

DETAILS OF AUTOPSIES

Patho-Anatomical Changes				
Cardiac Changes				
Certain or Suspected Rheumatic Changes		Coronary Sclerosis	Myocardial Fibrosis*	Other
Other				
Macroscopic	Microscopic			
0	Slight interstitial myocarditis	+	+	0
0	0	+	+	Lipomatosis
Pericardial adhesions	0	+	+	0
Acute pericarditis	Acute fibrotic pericarditis	+	+	Hypertrophy
0	0	+	0	Myeloid cells
0	0	+	0	Lipomatosis
Sclerosis, left ventricular valves	0	+	+	Left hypertrophy
Chronic pericardial adhesions	Benign chronic pericarditis Slight interstitial myocarditis	+	0	0
0	0	+	0	Hypertrophy Dilatation
Subacute fibrotic pericarditis	Subacute fibrotic pericarditis	+	+	0
Pericardial synechiae	Healed pericarditis	+	+	0
Pericardial synechiae	Chronic pericarditis Subacute interstitial myocarditis	+	0	0
0	Healed pericarditis	+	+	Brown atrophy

(6) Blocks from the right and left auricular walls in the region of the auricula cordis.

In some instances, parts of other organs were also microscopically examined.

The specimens were kept in a 10 per cent. formalin solution, embedded in paraffin, and stained with haematoxylin-eosin and haematoxylin-Van Gieson. The thickness of the slides was 10 μ. All the microscopic specimens were examined by one of us (F.W.). The results are shown in Table II.

Clinical.—This comprised 100 patients (23 male and 77 female; mean age 43 years) with typical rheumatoid arthritis, as well as a control group of 100 patients, 31 men (mean age 42 years) and 69 women (mean age 41 years). The age distribution was the same in both groups. No case of rheumatoid arthritis of less than 1 year's duration was included, and all cases with a definite or suspected earlier rheumatic fever were excluded. To eliminate cardiac changes originating in cardiosclerosis, patients of more than 60 years of age were avoided, and no case admitted to hospital because of cardiac disease, hypertension, pulmonary infection, diabetes, syphilis, or other disease that might affect the cardiovascular system was included. Cases of anaemia with haemoglobin values below 70 per cent. were also rejected. Of the 100 patients in the control group, 97 had been admitted to hospital and three treated in the out-patients' department for diseases with no significance from a cardiological or rheumatological point of view.

Investigations

Auscultation.—Only presystolic or diastolic murmurs were noted as pathological. When necessary, phonocardiography was applied to supplement the auscultation. Table III shows that the rheumatoid arthritis group contained only two pathological findings on auscultation, the control group none.

TABLE III
AUSCULTATORY FINDINGS

Sounds	Rheumatoid Arthritis	Controls
Normal heart sounds	46	78
Soft systolic murmurs	42	17
Harsh systolic murmurs	10	5
Presystolic or diastolic murmurs ..	2	0
Total	100	100

X Ray of the Heart.—Radiography was performed with contrast filling of the oesophagus. Volumes exceeding 500 ml. per sq. m. of body surface, and typical configuration changes were recorded as pathological findings. Each group contained one case with pathological findings. These two cases revealed relative heart volumes of 515 ml. without configuration defects.

Electrocardiography.—All were examined with extremity leads and chest leads. For technical reasons, only three chest leads were applied to a few patients (2 per cent.), but in most instances eleven, and in some up to twenty leads were used.

The following chest leads were used: Nebh leads (D, A, I, M), CR_2, IV R, CR_7, CR_8, CB_2, CF_2, and IV F. In addition, supplementary unipolar extremity leads and/or the chest leads of the Wilson series were applied.

The results were estimated in accordance with the schemata set forth by Grewin (1948). In the present investigation, an electrocardiogram with two or three estimated limit values was regarded as suspect, and one with more than three such values was classified as pathological. The results were as follows:

EXTREMITY LEADS ONLY

Rheumatic Group, 5 per cent. pathological (one man and four women), 6 per cent. suspect (one man and five women).

Control Group, 4 per cent. pathological (two men and two women), 2 per cent. suspect (one man and one woman).

CHEST LEADS ONLY

Rheumatic Group, none definitely pathological, 2 per cent. suspect (both women).

Control Group, 2 per cent. pathological (both women), 5 per cent. suspect (all women).

EXTREMITY AND CHEST LEADS TOGETHER

Rheumatic Group, 5 per cent. pathological, 7 per cent. suspect.

Control Group, 6 per cent. pathological, 7 per cent. suspect.

The two groups conformed fairly well, and these findings corresponded with those of Rohlin and Sundelin (1952). The changes are summarized in Table IV.

TABLE IV

ELECTROCARDIOGRAPHIC FINDINGS

Findings	Rheumatoid Arthritis	Controls
Numerous extra systoles	3	—
S–T–T changes	1	2
Bundle branch block	1	1
Pathological P waves	—	1
Pathological QRS	—	2

Hypoxaemia Test.—This was performed by the administration of 9 per cent. oxygen for 10 minutes. In judging the tests, the same criteria were applied as those used at the heart clinic at the Södersjukhuset in recent years, which represents a further degree of exactitude above the "strict criteria" of Levy and others (1941).

Tables V and VI disclose some peculiarities in the results of this test. In the rheumatoid arthritis group, one man and no less than seven women (8 per cent.) were unquestionably positive, and 2 per cent. were suspect (one man and one woman); in the control group only 4 per cent. were positive and 2 per cent. were suspect (one of the latter also had a suspect electrocardiogram).

TABLE V

RESULTS OF HYPOXAEMIA INVESTIGATIONS

Test Results	Positive			Suspect		
Sex	Male	Female	Total per cent.	Male	Female	Total per cent.
Rheumatoid Arthritis ..	1	7*	8	1	1*	2
Controls ..	0	3	3	1	1	2

* All had normal electrocardiograms except one female rheumatoid patient and one female control.

TABLE VI

POSITIVE FINDINGS IN RHEUMATOID ARTHRITIS AND CONTROL GROUPS

Group	Sex	Age (yrs)	Pre-systolic Murmur	*X* ray	Electro-cardio-gram	Hypo-xaemia Test
Rheumatoid Arthritis (14)	M	58	—	—	—	+
	F	54	—	—	—	+
	F	53	—	—	+	—
	F	53	—	—	—	—
	M	50	—	+	—	—
	F	48	—	—	—	+
	F	44	—	—	—	+
	F	44	—	—	+	—
	M	43	—	—	—	—
	F	42	—	—	+	—
	M	39	—	—	+	—
	F	34	—	—	—	+
	F	33	—	—	—	+
	F	28	—	—	+	+
	Total ..		2	1	5	8
Control (11)	F	56	—	—	—	+
	F	52	—	—	+	—
	M	49	—	—	+	—
	F	43	—	—	—	+
	M	41	—	+	—	—
	M	39	—	—	+	—
	F	35	—	—	—	+
	F	34	—	—	+	—
	F	34	—	—	+	—
	F	33	—	—	+	—
	F	12	—	—	—	+
	Total ..		0	1	6	4

The positive findings in all these tests may be summarized as follows:

Rheumatoid Group	Presystolic murmur over the apex	2	14* per cent.
	Pathological radiograph of the heart	1	
	Abnormal electrocardiograms	5	
	Positive hypoxaemia test	8	

* Two cases showed two results each.

Control Group	Abnormal auscultation findings	0	11 per cent.
	Pathological radiograph of the heart	1	
	Abnormal electrocardiograms	6	
	Positive hypoxaemia test	4	

Discussion

It was not easy to assemble a large number of cases for *post-mortem* investigation of the occurrence of cardiac lesions in patients with rheumatoid arthritis. Since we excluded cases not available for personal examination, our material is rather small, although we have been considering the present problem from as far back as 1940.

In the reports of earlier investigators, the percentages of rheumatic heart changes vary considerably, even when patients with rheumatic fever, or other diseases affecting the heart, are excluded. Young and Schwedel (1944), Baggenstoss and Rosenberg (1941), Rosenberg, Baggenstoss, and Hench (1944), and Graef, Hickey, and Altmann (1949) gave high incidence of pathological findings, but Clark and Bauer (1948), Bywaters (1950), and Sokoloff (1953) reported a low incidence. It is possible that due regard was not always paid to senile changes.

The negative results of the present investigation are partly to be explained by the fact that all cases of rheumatic fever were excluded. Pericarditis, healed or not, was ascertained in seven cases, *i.e.* in more than half the autopsy material. Inflammatory conditions in the lungs and kidneys, which may have contributed to the pericarditis, were noted in some of them, but the frequency of pericarditis in the present material is such that it may, perhaps, be adduced in favour of the contention of Sokoloff and other workers that this condition may be a cardiac manifestation of rheumatoid arthritis. Some of the autopsy cases also showed changes which were interpreted as due to age. Mainland (1953) has summarized factors which have to be borne in mind in any analysis of hospital material, and hospitalization itself implied a selection. In the present investigation the elimination of all cases with cardiac disease as a principal reason for admission may have caused too low a percentage of pathological cardiac findings in the rheumatoid series.

Baggenstoss and Rosenberg (1944) described two cases with cardiac changes markedly suggestive of rheumatic nodules. Sokoloff (1953) discussed the possible occurrence of a specific rheumatoid heart disease, characterized by inflammatory tissue lesions similar to those seen in subcutaneous rheumatic nodules. He studied two such cases, and also referred to similar findings by Graef, Hickey, and Altmann (1949), who described two cases with changes of a nodular type, as well as two cases with changes in the coronary vessels similar to those seen in periarteritis nodosa. Clark and Bauer (1948) and Gruenwald (1948) observed similar nodular changes, but those described by Bevans and others (1954) may be of a different type. Cruickshank (1954) found arteritis, past or present, in eighteen of 72 fatal cases of rheumatoid arthritis; in seven of these, "lesions diagnostic of rheumatic heart disease were also found and the vascular involvement was mainly confined to the heart".

The present authors have noted no such changes, however.

As far as auscultatory, radiological, and (ordinary) electrocardiographic findings are concerned, no difference was noted between the rheumatoid arthritis group and the control group.

On the other hand, the results of the hypoxaemia test showed 8 per cent. positive and 2 per cent. suspect in the rheumatoid group, and only 4 per cent. positive and 2 per cent. suspect in the control group, and most of these were seen in subjects with normal electrocardiograms.*

The age of the female patients with positive hypoxaemia tests and normal electrocardiograms varied in the rheumatoid group of the present material from 33 and 34 to 44, 48, 53, and 54 years, and in the control group from 12 to 35, 43, and 56 years. There was thus no difference in age.

One patient treated with cortisone gave a positive hypoxaemia test, but in two other similar cases the result was normal.

It is thus difficult to assess the significance of positive hypoxaemia tests in rheumatoid arthritis. Positive hypoxaemia tests and/or definite electrocardiographic changes occurred with roughly the same frequency in both groups.

Rheumatoid arthritis group:	7 + 5 = 12 per cent.
Control group:	4 + 6 = 10 per cent.

* 7 per cent. (one man and six women) of the rheumatoid patients had normal electrocardiograms and pathological hypoxaemia tests, and both the rheumatoid patients with "suspect" hypoxaemia tests had normal electrocardiograms. In the control group all four with pathological and one of the two with suspect hypoxaemia tests had normal electrocardiograms.

If the "suspect" cases are included, the results are still closely similar:

Rheumatoid arthritis group: 12 + 10 = 22 per cent.
Control group: 10 + 8 = 18 per cent.

It is therefore necessary to seek an explanation of the positive hypoxaemia tests other than that they are due to cardiac affections:

(1) *Physical Inactivation.*—Prolonged confinement to bed or restricted mobility due to rheumatoid arthritis may lower the tolerance of circulatory exertion so as to preclude a normal adjustment reaction.

None of our patients was in such a condition as to render this explanation probable.

(2) *Anaemia.*—A pronounced anaemia may cause a positive hypoxaemia test, but the condition is reversible, in so far as rising blood values restore normality.

As previously stated, patients with haemoglobin values below 70 per cent. were eliminated, to avoid this source of error. However, two patients in the rheumatoid group who gave positive hypoxaemia results showed blood values only just above this limit and had periodically displayed lower values; in these two subjects the anaemia may have caused the positive hypoxaemia tests.

(3) *Internal Secretion.*—Positive hypoxaemia tests may often be noted in women at the age of puberty and in the years immediately following; as well as at the climacteric. These are probably not caused by any cardiac affection; the symptoms may be only temporary, and most likely originate in some vegetative vascular mechanism.

Summary

The literature on cardiac changes in rheumatoid arthritis is summarized. Most pathological investigations recorded high percentages of cardiac changes of a rheumatic nature, the frequency of such changes in clinical investigations being much lower. Possible explanations of this discrepancy are discussed. In some earlier series, the authors may have failed to pay proper attention to previous rheumatic fever, intercurrent disease of a cardiological character, or changes due to old age.

The present investigation is divided into pathological and clinical sections.

In thirteen *post-mortem* cases, none manifested any signs of rheumatic endocarditis. Changes, such as those characterized by Sokoloff as indicative of rheumatoid heart disease, were not noted. Signs were found of pericarditis, healed or not, in seven of the thirteen cases, which supports the assumption of certain authors that pericarditis may constitute a cardiac manifestation in rheumatoid arthritis. However, in some of these seven cases other concurrent diseases may have originated the pericarditis.

The clinical series consisted of one hundred cases of rheumatoid arthritis, and one hundred control cases of the same age and sex distribution. No case with a history of rheumatic fever or other disease of cardiological importance was included. The investigation comprised auscultation, phonocardiography, radiography of the heart, electrocardiography (with three standard leads and, in practically all cases, at least eleven chest leads), and hypoxaemia tests.

When the positive findings from auscultation, phonocardiography, radiography, and electrocardiograms are taken together, they produce a final result amounting to 8 per cent. for the rheumatoid group and 7 per cent. for the control group.

In the present series, therefore, patients suffering from rheumatoid arthritis did not manifest any increased frequency of endocardiac or myocardiac changes which might be due to the arthritis. In our opinion the endocardium and the myocardium are only slightly affected in rheumatoid arthritis, though inflammation of the pericardium may, perhaps, be not infrequent.

In support of the idea of a close relationship between rheumatoid arthritis and rheumatic fever, several authors have pointed to the high frequency of cardiac changes of a rheumatic nature which may be found in cases of rheumatoid arthritis, implying that these two diseases are manifestations of the same basic illness. But the results of the present investigation indicate that, when the cardiac findings only are taken into account, rheumatic fever and rheumatoid arthritis should be regarded as two distinct diseases.

The only significant difference was found in the results of the hypoxaemia tests; positive results being more frequent in the rheumatoid group.

These examinations were performed at the *X*-Ray Dept. II, to the head of which, W. Magnusson, M.D., special thanks are due.

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Lésions cardiaques dans l'arthrite rhumatismale

RÉSUMÉ

On récapitule la littérature sur les lésions cardiaques dans l'arthrite rhumatismale; la plupart des recherches anatomo-pathologiques en révèlent des pourcentages élevés, tandis que les études cliniques donnent des chiffres bien inférieurs. On discute les raisons probables de cette divergence et on croit que dans des observations plus anciennes les auteurs auraient pu ne pas porter attention suffisante sur le rhumatisme articulaire aigu, les maladies intercurrentes de caractère cardiologique ou les lésions séniles.

L'enquête présente se divise en parties anatomo-pathologique et clinique.

Dans treize cas d'autopsie on ne trouva pas de signes d'endocardite rhumatismale. On ne vit pas de lésions qui, d'après Sokoloff, indiqueraient la maladie rhumatismale du coeur. On trouva, par contre, des signes de péricardite, cicatrisée ou non, dans sept cas sur treize, ce qui vient à l'appui de l'hypothèse de certains auteurs que la péricardite peut constituer une manifestation cardiaque de l'arthrite rhumatismale. Dans certains de ces sept cas, cependant, d'autres maladies concurrentes auraient pu causer la péricardite.

La partie clinique comportait cent cas d'arthrite rhumatismale et cent témoins d'âges et de sexes correspondants. Des cas avec antécédents de rhumatisme articulaire aigu ou de toute autre maladie d'importance cardiologique n'y étaient pas inclus. L'examen comportait l'auscultation, la phonocardiographie, la radiographie du coeur, l'électrocardiographie (avec trois dérivations habituelles et, presque toujours, avec au moins onze dérivations thoraciques) et des épreuves d'hypoxémie.

L'ensemble des résultats positifs d'auscultation, de phonocardiographie, de radiographie et d'électrocardiographie donne le chiffre final de 8 pour cent pour les rhumatisants et de 7 pour cent pour les témoins.

Dans cette série donc, la fréquence des lésions de l'endocarde ou du myocarde chez les rhumatisants n'était pas assez élevée pour qu'on puisse l'attribuer à l'arthrite. A notre avis, dans l'arthrite rhumatismale l'atteinte du myocarde ou de l'endocarde n'est que légère, bien que la péricardite pourrait être plus fréquente.

A l'appui de la conception qu'il y aurait un rapport étroit entre l'arthrite rhumatismale et le rhumatisme articulaire aigu, plusieurs auteurs ont signalé la grande fréquence des lésions cardiaques de nature rhumatismale trouvables dans des cas d'arthrite rhumatismale, signifiant ainsi qu'il s'agirait de manifestations diverses de la même maladie. L'enquête présente indique, toutefois, qu'en tenant compte des résultats cardiologiques seulement, le rhumatisme articulaire aigu et l'arthrite rhumatismale doivent être considérés comme deux maladies distinctes.

La seule différence significative fut trouvée dans les résultats de l'épreuve d'hypoxémie, les positifs étant plus fréquents chez les rhumatisants.

Lesiones cardiacas en la artritis reumatoide

SUMARIO

Se resume la literatura sobre las lesiones cardiacas en la artritis reumatoide. La mayoría de las investigaciones anatomo-patológicas revela altos porcentajes de tales lesiones, las investigaciones clínicas dando cifras mucho más bajas. Se discute las razones probables de esta divergencia y se supone que en ciertas estadísticas anteriores los autores no prestaron atención suficiente al reumatismo poliarticular agudo, a las enfermedades intercurrentes de carácter cardiológico o a las lesiones seniles.

La investigación presente se divide en parte anatomo-patológica y clínica.

En trece casos de autopsia no encontráronse signos de endocarditis reumática. Tampoco se notaron lesiones que, según Sokoloff, indicarían le enfermedad reumática del corazón. Hubo, en cambio, manifestaciones de pericarditis, activa o curada, en siete de los trece casos, lo que soporta la teoría de ciertos autores según la cual la pericarditis pudiera constituir una manifestación cardiaca de la artritis reumatoide. En algunos de estos siete casos, sin embargo, otras enfermedades concurrentes habrían podido motivar la pericarditis.

La parte clínica comprende cien casos de artritis reumatoide y cien testigos de edades y sexos correspondientes. Casos con antecedentes de reumatismo poliarticular agudo o de otra enfermedad cualquiera de importancia cardiológica no fueron incluídos. La investigación comprendió: auscultación, fonocardiografía, radiografía del corazón, electrocardiografía (con tres derivaciones usuales y, virtualmente en todos los casos, con trece derivaciones torácicas) y con reacciones de hypooxemia.

El conjunto de los resultados positivos de auscultación, fonocardiografía, radiografía y electrocardiografía da la cifra final de 8 por ciento para los reumáticos y de 7 por ciento para los testigos.

En esta serie, pues, la frecuencia de las lesiones del endocardio y del miocardio en los reumáticos no fué suficiente para poder atribuirla a la artritis. Nos parece que el compromiso del miocardio o del endocardio en

la artritis reumatoide es muy leve y el del pericardio, quizás, más frecuente.

En apoyo de la idea de una relación estrecha entre la artritis reumatoide y el reumatismo poliarticular agudo, varios autores señalaron la gran frecuencia de las lesiones cardíacas de naturaleza reumática que se pueden encontrar en los casos de artritis reumatoide, implicando que se trataría de manifestaciones diferentes de la misma enfermedad. La investigación presente indica, sin embargo, que con tener cuenta sólo de los resultados cardiológicos, el reumatismo poliarticular agudo y la artritis reumatoide deben considerarse como enfermedades distintas.

La única diferencia significativa fué encontrada en los resultados de la reacción de hipooxemia, siendo los positivos más frecuentes en los reumáticos.

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HUMAN SKIN COLLAGEN FROM DIFFERENT AGE GROUPS BEFORE AND AFTER COLLAGENASE DIGESTION

AN ELECTRON MICROSCOPIC STUDY*

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That some alteration in collagen occurs with age has been indicated by various workers. Young rat tendon (Neuberger and others, 1951) shows a greater radioactive glycine turnover than that of adult animals. Similar findings were reported in the skin of rats (Neuberger and Slack, 1953) and rabbits (Harkness and Neuberger, 1952). Under the electron microscope the collagen fibres in newborn rat skin were shown to be narrower than in older rats (Gross, 1950). Human skin, tendon, and dura collagen was found to vary in extractability with dilute acid according to age, being more soluble below the age of one year (Banfield, 1952). The excretion of hydroxyproline in children was significantly greater than in adults (Ziff and others, 1954), indicating the presence of an increased pool of hydroxyproline peptide for collagen synthesis in the growing individual. The authors found no difference between patients with or without collagen disease. Previous chemical studies (Keech, 1954a) showed a significant difference in digestion between the skin collagen of infants and adults following incubation with collagenase, but again no difference between patients with or without collagen disease.

It appeared to be of interest to find out whether collagen from different age groups differs in its response to collagenase, and whether there is any correlation with different types of disease, particularly "collagen disease". This paper describes the effect (macroscopic and electron microscopic) of collagenase on extracted human skin collagen from sixty individuals of all ages dying from a variety of causes. In addition, some changes in the untreated skin of non-incubated controls are included, as these may lead to a better understanding of the structure of collagen fibrils.

Materials and Methods

I. Incubated Controls and Collagen Incubated with Collagenase

Collagenase obtained from *Cl. histolyticum* was kindly supplied by Dr. J. D. MacLennan, the same batch being used throughout. It contains a very small quantity of proteinase, but is the purest preparation available, as a crystalline form has yet to be made.

Unfixed, frozen autopsy abdominal skin from the left upper quadrant was thawed, the dermis minutely dissected out and the collagen extracted by a shortened form of the method of Neuman (1949a, b), as previously described (Keech, 1954a). 20 mg. (dry weight) were incubated with collagenase (0·1 ml. of a 0·5 per cent. solution or 0·1 mg. enzyme nitrogen) and 0·05 ml. penicillin and streptomycin mixture in a total volume of 5 ml. phosphate buffer (*p*H 7·3) for 24 hrs at 37° C. Control tubes were treated in the same way, including the antibiotic mixture but without enzyme (Fig. 1, overleaf).

The first two cases were examined at 10 min. and ½, 1, 1½, 2, 3, and 24 hrs, and showed a gradual transition to the 24-hr picture. After this standard intervals of 10 or 60 min., 3 and 24 hrs were chosen as giving representative information for all age groups. The approximate macroscopic digestion as compared with the control tube was recorded, and drops of the suspension after shaking were taken for electron microscopic examination. The drops were placed on collodion-covered 200 mesh Cu-Ni grids, allowed to dry, washed for 15 min. in de-mineralized distilled water, shadowed with palladium, and examined in the RCA Model EMU 2 A electron microscope.

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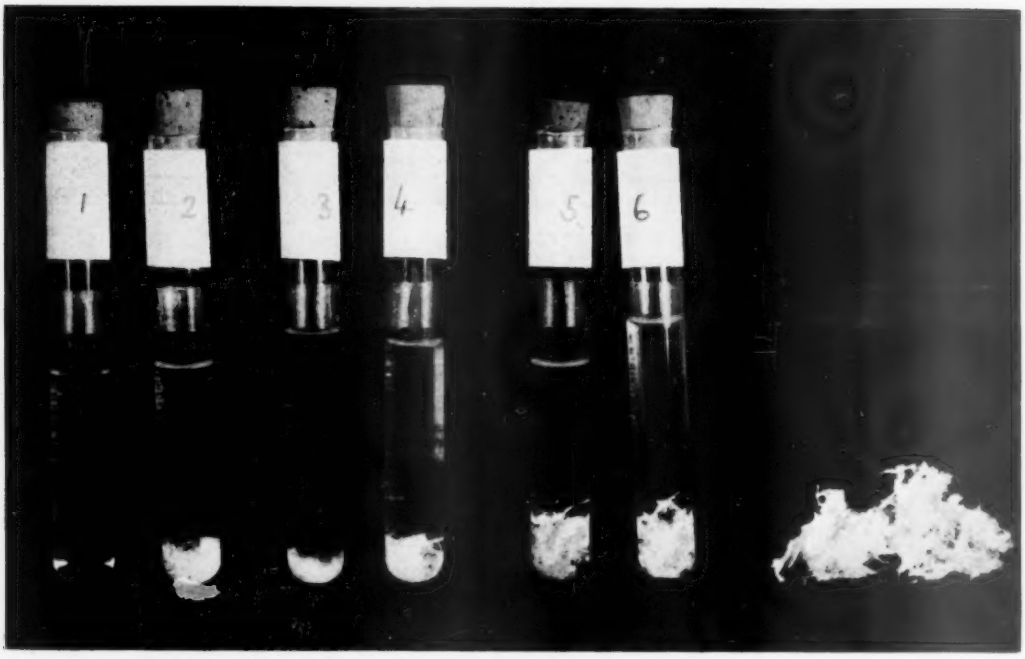


Fig. 1.—Extracted skin collagen after incubation with collagenase at 37° C. for 24 hrs. Tubes 2, 4, and 6 are controls.
Tube 1.—From a 17-year-old patient dying of lymphocytic lymphoma, showing complete digestion.
Tube 3.—From a 43-year-old patient dying of uraemia; about 50 per cent. digested.
Tube 5.—From an 18-year-old patient with congenital heart disease showing no digestion.
On the extreme right is a sample of extracted skin collagen. Before incubation each tube contained 20 mg. dry weight of substrate in 5 ml. phosphate buffer at *p*H 7·3.

II. Untreated Collagen

The early stages of collagen extraction (*vide supra*) entailed homogenizing the dissected, unfixed dermis in de-mineralized distilled water in a Waring blendor in the cold room for 15 min. The final temperature of the solution was 30° C. or less in each case. Drops of this suspension were examined under the electron microscope as a routine in addition to the incubated collagen-in-buffer controls already described.

Results

I. Incubated Controls and Collagen Incubated with Collagenase

Normally collagen fibrils are long, passing right across the microscopic field, and it is unusual to see the fibril ends. After homogenization in a Waring blendor, scanty, blunt, or torn ends are seen (Fig. 2, opposite).

Collagen incubated in buffer without enzyme presented this unaltered appearance.

A. Macroscopic Digestion.—There was a marked difference with respect both to age and to incubation time. The collagen from infants and children digested more rapidly than that of adults (Fig. 3, overleaf).

100 per cent. digestion was considered to have occurred when no solid collagen was visible at the bottom of the test tube (Fig. 1). At 3 hrs the average digestion per age group showed a steady decline with increase in age. At 24 hrs 80 to 90 per cent. of the collagen had disappeared from individuals under 40 years of age. Above this age there was a significant fall, an average of only 19 per cent. digesting in the same time. The readings in each group were remarkably consistent apart from the few exceptions discussed below. In eight cases, examination after 6 hrs' incubation revealed practically the same macroscopic and microscopic picture as at 3 hrs, except in one man aged 52 dying from carcinoma of the lung. About 5 per cent. of this collagen had disappeared by 3 hrs, 70 per cent. at 6 hrs, and 90 per cent. at 24 hrs, with a corresponding change in microscopic components.

Exceptions (excluded from Fig. 3, overleaf)

(*a*) *Absent Digestion.*—In eight individuals the collagen did not digest (Table, overleaf, and Fig. 1).

Throughout this study batches of four to eight cases were incubated together, common buffer and enzyme solutions being used for all tubes. At 24 hrs the occasional exception was prominent compared with the partially or completely digested contents of adjacent

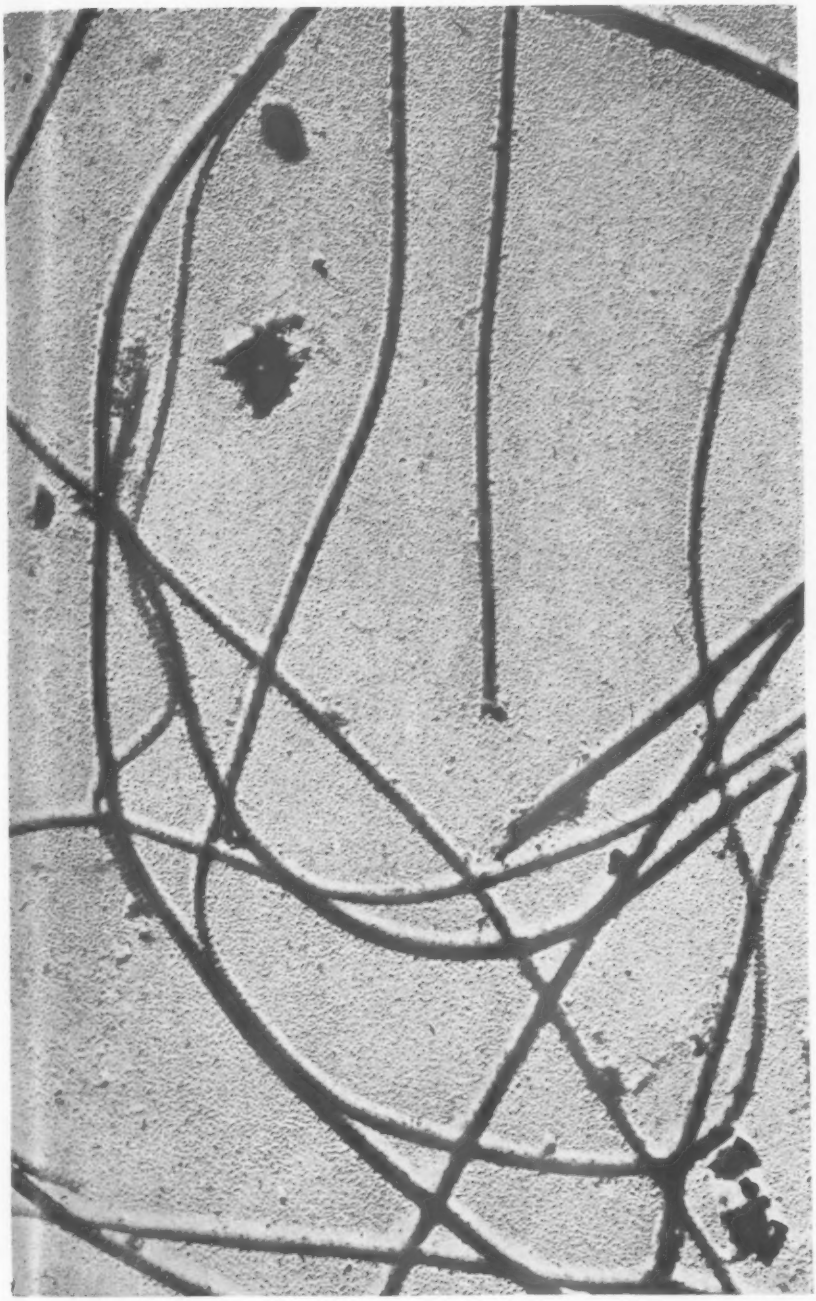


Fig. 2.—Control picture of skin collagen from a 9-year-old boy dying from dermatomyositis, after homogenizing in de-mineralized, distilled water. Note variation in fibril size, the fibrils passing right across the field, with scanty, blunt ends produced by the Waring blendor. Some amorphous material is present. × 14,800

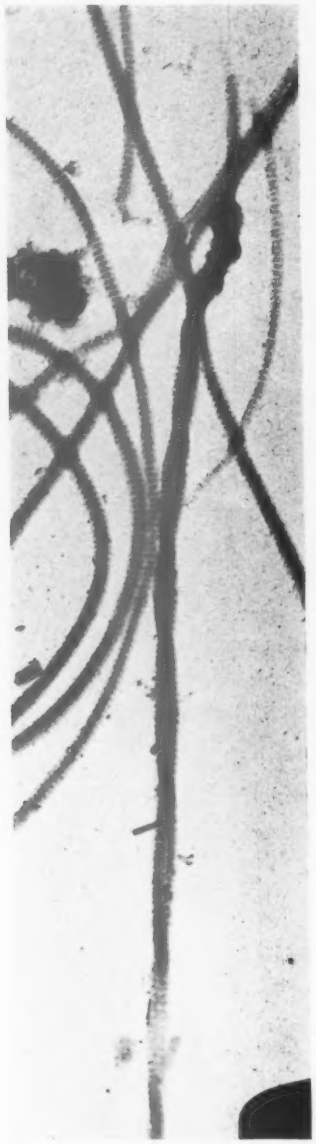


Fig. 2(*a*).—Collagen from same case as Fig. 2 to show true twisting of the fibrils (cf. Figs 28 and 29). × 7,400.

NOTE: All the electron micrographs are shadowed with palladium.

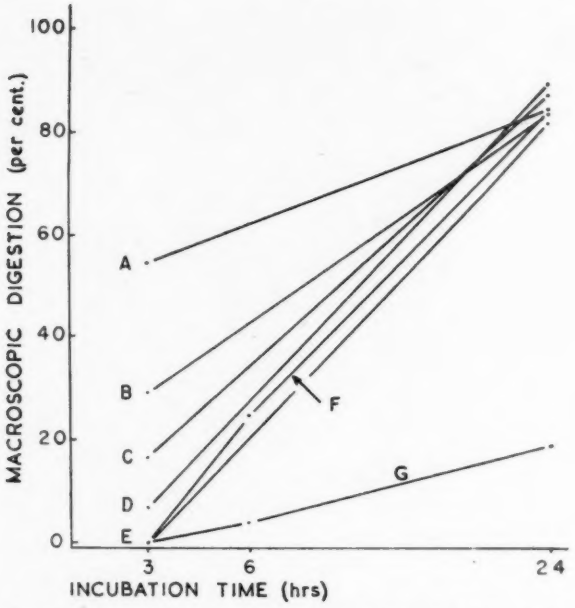


Fig. 3.—Per cent. macroscopic digestion of abdominal skin collagen from 51 cases with and without "collagen disease" after incubation with collagenase at 37° C.

KEY TO FIGURE 3.

Graph	Age Group	No. of Cases	Incubation Time (hrs) 3 Average	3 Range	6 Average	6 Range	24 Average	24 Range
A	NB+EF*	12	55	20-80			85	70-95
B	1-6 mths	4	30	20-60			84	85-90
C	1-10 yrs	17	17	5-40			88	80-95
D	11-20 yrs	7	7	0-10			90	85-95
E	21-30 yrs	5	0	0			82	50-95
F	31-40 yrs	2	0	0	25	20-30	85	80-90
G	41-50 yrs	4	0	0	4	0-10	19	10-25

* NB+EF newborn+erythroblastosis.

tubes. Even though the activity of the solutions was without question, a large amount of collagenase was added to one such tube and incubated for a further 46 hrs, but the collagen remained unaltered.

(*b*) *Excessive Digestion.*—This occurred in the case of a 20-year-old patient with fulminating acute rheumatic carditis, and in a 52-year-old man with carcinoma of the lung who had received intravenous nitrogen mustard for the 4 days before his death. Both these gave readings comparable to those in children under one year old.

Cases of Collagen Disease.—Included in the series forming the basis of this report were eight cases of collagen disease. These gave the following results:

Dermatomyositis.—The macroscopically normal abdominal skin from one 9-year-old patient digested normally, whereas rash-bearing axillary skin from the same patient and the normal abdominal skin from a 5-year-old did not digest at all (Table).

TABLE

EXCEPTIONS EXCLUDED FROM FIG. 3

Age (yrs)	Diagnosis	Macroscopic Digestion (24 hrs)
1½	Acute leukaemia	Nil
5	*Dermatomyositis	Nil
9	†Dermatomyositis	Nil
9½	Mental deficiency, Sepsis	Nil
13	Juvenile rheumatoid arthritis	Nil
18	Congenital heart disease, Pulmonary vascular sclerosis	Nil
43	Diabetes mellitus for 15 yrs, Kimmelstiel-Wilson's disease and glaucoma	Nil
51	Hypertension, Subarachnoid haemorrhage	Nil
20	Acute rheumatic carditis	3 hrs (60 per cent.) 24 hrs (90 per cent.)
52	Carcinoma of lung	6 hrs (70 per cent.) 24 hrs (90 per cent.)

* Abdominal skin.

† Rash-bearing axillary skin. Abdominal skin from the same case digested normally.

Juvenile Rheumatoid Arthritis.—In one patient with typical widespread deformities, who had received large doses of cortisone for 3 months before death, collagen digestion was absent (Table).

Rheumatic Heart Disease.—The excessive digestion of one fulminating case is described above. One patient with subacute bacterial endocarditis super-imposed on rheumatic heart disease and one dying of chronic rheumatic heart failure conformed both macro- and microscopically to their age groups.

Disseminated Lupus Erythematosus.—Two cases exhibited the average digestion for their age groups.

Polyarteritis Nodosa.—One case exhibited the average digestion for the age group.

B. Electron Microscopic Findings.—Collagen incubated in buffer without enzyme (controls) remained unaltered. The crystalline residue from buffer alone and collagenase in buffer (following the usual

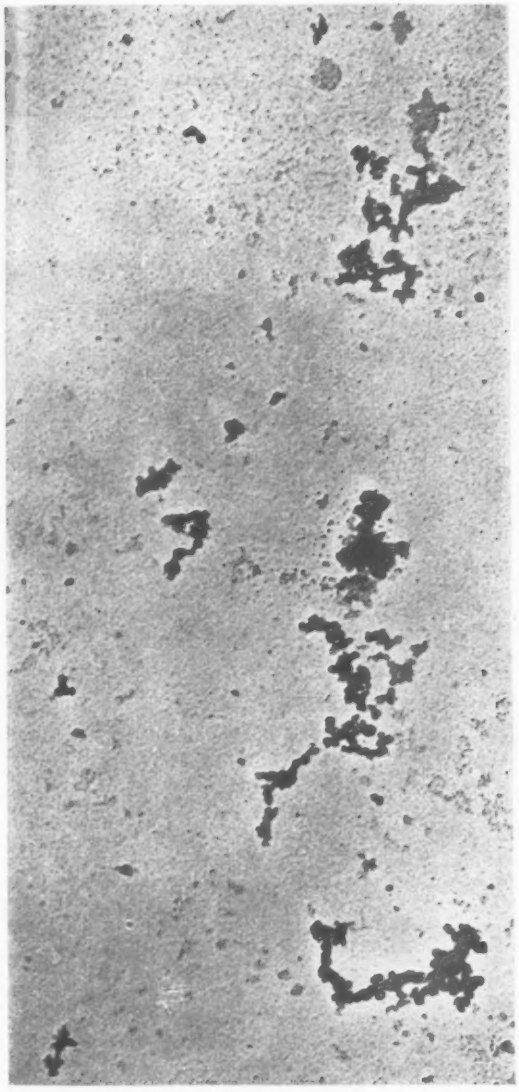


Fig. 4.—Phosphate buffer alone after 3 hrs incubation at 37° C. × 28,000.

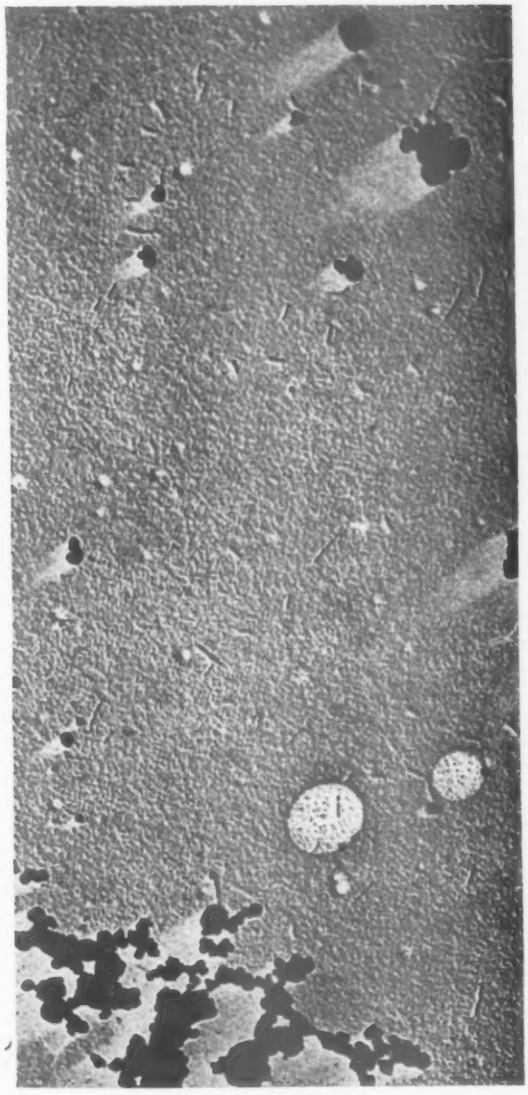


Fig. 5.—Collagenase in buffer after 3 hrs at 37° C. There are many short fibres believed to represent the enzyme protein. × 24,000.

preparation for electron microscopic examination) are shown in Figs 4 and 5. The latter contains short rods, termed "enzyme fibres", presumed to be enzyme protein and analogous to the fibrous structures arising from solutions of purified, crystallized trypsin (Gross, 1951). These can be easily distinguished from the beaded fibrils and granular debris described below (Fig. 6, overleaf).

In collagen incubated with collagenase, three classes of structure were seen as well as minute beaded fibrils and "beads". All these elements may be present together or separately in the same grid or field, the proportions varying according to age and length of incubation.

(1) "*Standard*" *Collagenase Change*.—This denotes the alterations described by Gross (1953) in cow-hide corium collagen, and by Keech (1954b) in abdominal skin from a 73-year-old adult, *i.e.* separation of the bundle fibrils, tapering of the fibril ends, and localized narrowings in the fibre

Fig. 6.—Skin collagen from a 15-year-old patient dying of a fractured skull. Preparation incubated with collagenase for 1 hr. The enzyme fibres can be clearly distinguished from the beaded fibrils and granular debris. × 22,200.

width with separation to form tactoids (short lengths of striated collagen tapered at both ends). There is no observable distortion of axial periodicity and no swelling of the fibrils (Fig. 7; also Fig. 10, overleaf).

Fig. 7.—Skin collagen from a 52-year-old man dying of carcinoma of the lung. Preparation incubated for 6 hrs with collagenase. Striated fibres showing "standard" collagenase change, some of which appear to be disintegrating into finely beaded material. This illustrates localized, through-the-bundle points of enzyme action, producing narrowings in the fibril width and tactoids. Note that there is no observable distortion of the axial periodicity and no swelling of the fibrils. × 12,700.

Fig. 8.—Skin collagen from a 3-year-old child dying with pulmonary arteriolosclerosis. Preparation incubated for 3 hrs with collagenase. This shows finely striated (210 Å) fibrils mixed in with others bearing the usual 640 Å band. × 26,000.

Fig. 9.—Skin collagen from a 7-year-old child dying from Hodgkin's disease. Preparation incubated with collagenase for 1 hr. The fibril illustrated has 640 Å banding in its wider part and 210 Å striations in its narrower termination. × 28,000.

Thin, finely striated collagen fibrils (210 Å) were seen to be mixed in with larger fibrils bearing the usual 640 Å band (Figs 8 and 9).

Some fibrils bore 640 Å periods in their wider part and 210 Å in their long, narrow terminations (Fig. 9). Wyckoff (1949) noted that this phenomenon occurred occasionally in the Achilles tendon in animals. Finely striated fibrils with an axial periodicity one-third of the usual period have been described in animal collagen (paramuscular connective tissue from a mature rabbit; adult dog's heart tendon) as well as in re-precipitated collagen (Vanamee and Porter, 1951; Wyckoff, 1952).

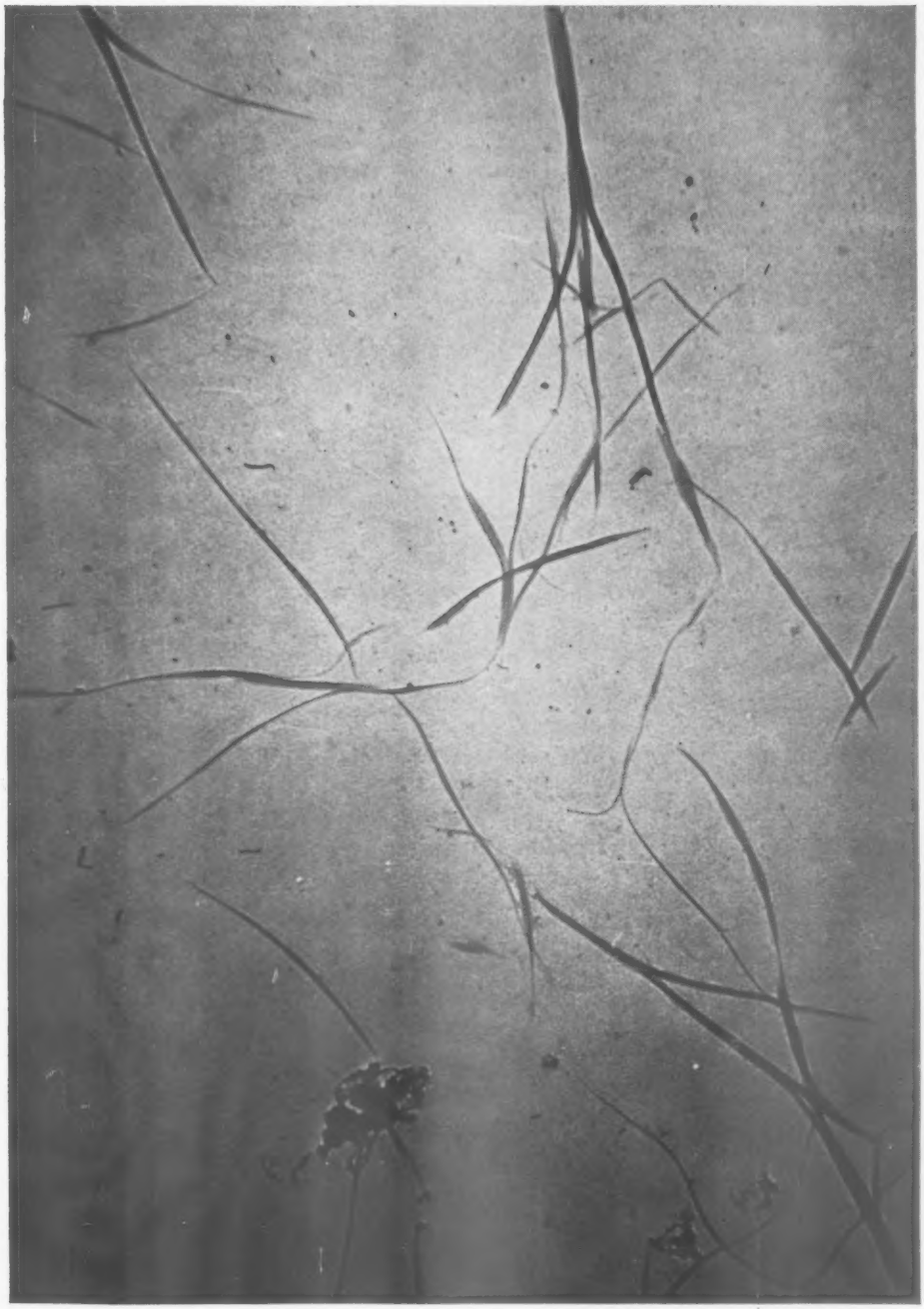


Fig. 10.—Skin collagen from a 28-year-old patient dying from coronary thrombosis. Preparation incubated with collagenase for 1 hr. Striated collagen showing "standard" collagenase change, *i.e.* separation of the bundle fibrils, tapering of the fibril ends, and localized narrowings in fibril width with separation to form tactoids. Tactoids are short lengths of striated collagen tapered at both ends. × 6,900.

(2) "*Moth-eaten*" *Fibres.*—Large, very dense bundles of collagen presented a striking moth-eaten appearance on the microscope screen (Figs 11-17, overleaf). These dense bundles were segmented, the non-opaque areas frequently showing striated fibrous "links" indicating the true origin of the structure.

Fig. 11.—Skin collagen from an 11-year-old child dying from polyarteritis nodosa. Preparation incubated with collagenase for 24 hrs. Typical "moth-eaten" fibre consisting of a dense bundle of swollen, segmented collagen, the segments being joined by fibrous "links" indicating the true origin of the structure. × 22,500.

Fig. 12.—Enlargement of a striated fibrous "link" from a 9-year-old mentally deficient child. The collagen had been incubated with collagenase for 24 hrs. × 23,000.

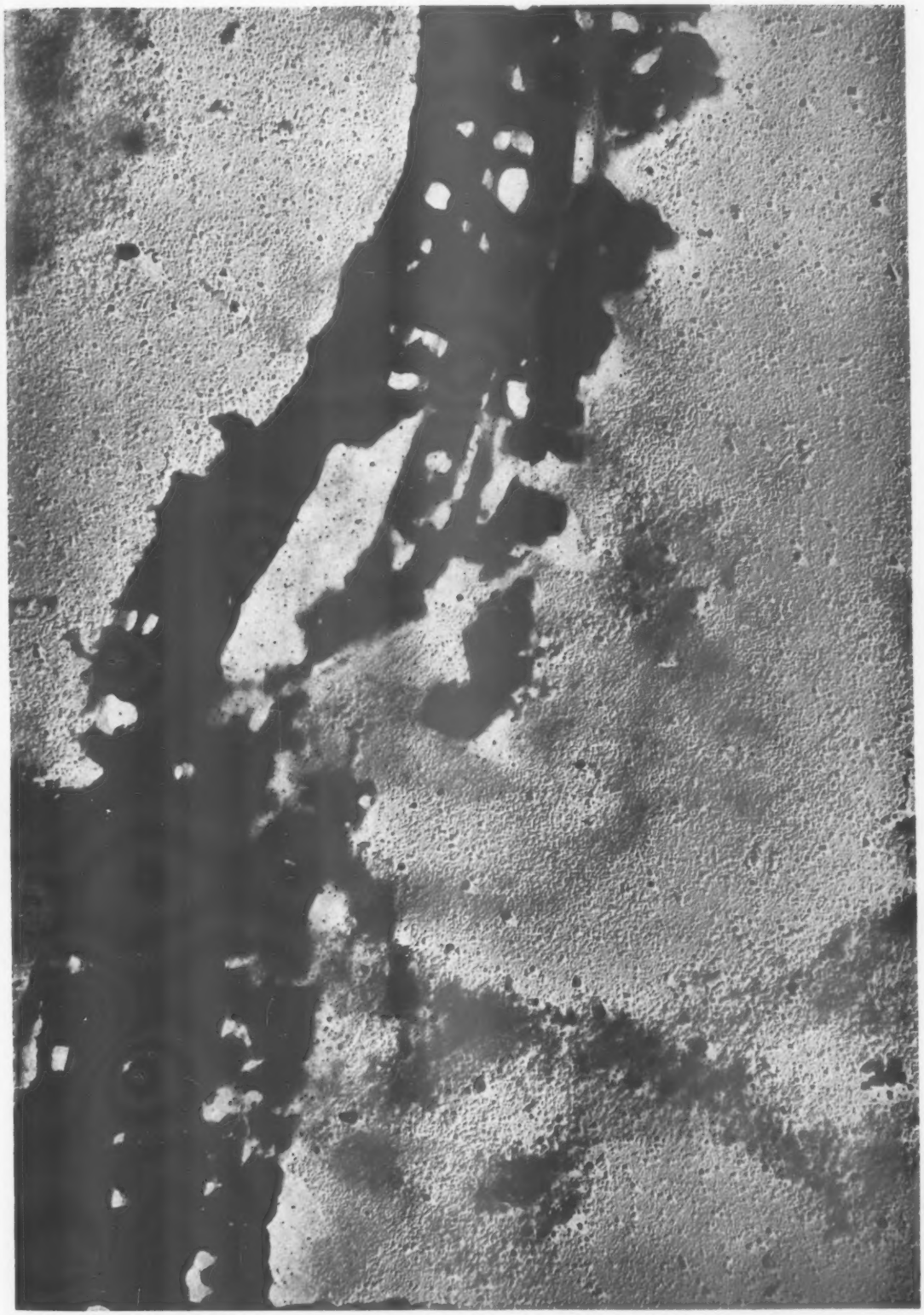


Fig. 13.—Collagen from macroscopically normal skin from a 12-year-old child dying from disseminated lupus erythematosus. Preparation incubated with collagenase for 24 hrs. "Moth-eaten" fibre apparently disintegrating into clouds of "beads". × 15,000.

Fig 14.—Skin collagen from a 5-year-old child dying from a nasopharyngeal tumour. Preparation incubated with collagenase for 3 hrs. A group of "moth-eaten" fibres apparently disintegrating into masses of long beaded fibrils and "beads". × 10,000.

Fig. 15.—Skin collagen from a 5-year-old child dying from a nasopharyngeal tumour. Preparation incubated with collagenase for 3 hrs. "Moth-eaten" fibre showing basic fibrous structure. Note several long-beaded fibrils. × 11,600.

Fig. 16.—Skin collagen from a leukaemic 4-year-old child. Preparation incubated with collagenase for 3 hrs. Early stage of a "moth-eaten" fibre, where some striated fibrils still remain. × 20,500.

Fig. 16 shows an early stage where some striated fibrils still remain. Fig. 17 (overleaf) shows another fibre apparently disintegrating into its constituent "beads".

Fig. 18.—Skin collagen from a newborn infant dying from erythroblastosis foetalis. Preparation incubated with collagenase for 30 min. Typical "granular degenerating" fibre. × 6,500.

Fig. 17.—Skin collagen from a 2-year-old child dying from α-γ-globulinaemia and bronchopneumonia. Preparation incubated with collagenase for 3 hrs. "Moth-eaten" fibre apparently disintegrating into constituent "beads". × 12,500.

Fig. 19.—Same as Fig. 18. × 16,500.

(3) "*Granular Degenerating*" *Fibres*.—These were characteristically seen in child's or infant's enzyme-treated collagen, the microscopic fields being filled with thick granular bundles bearing none of the features of striated collagen. The bundles were so thick that their granular nature could only be observed at the edge, or in thinner, flatter bundles (Figs 18 and 19).

Fig. 20.—Collagen from macroscopically normal skin from a 9-year-old child dying of dermatomyositis. Preparation incubated with collagenase for 24 hrs. Disintegrating "moth-eaten" fibres, some granular debris, "beads", and long beaded fibrils. Most of the latter are lined up in register to form a skeleton fibre. × 16,400.

Fig. 21.—Skin collagen from a 5-year-old child dying from a nasopharyngeal tumour. Preparation incubated with collagenase for 3 hrs. "Moth-eaten" fibres, numerous long-beaded fibrils, and "beads". The axial periodicity of the beaded fibrils "fit in" with the banding of the two striated collagen fibrils present. × 18,800.

Fig. 22.—Collagen from macroscopically normal skin from a 9-year-old child dying of dermatomyositis. Preparation incubated with collagenase for 3 hrs. Transformation of striated collagen into an early "granular degenerating" fibre. × 16,200.

However, early stages were found (Fig. 22) illustrating the conversion of striated collagen into these well-defined "bands" or "ribbons" of granular material. Later in the incubation

Fig. 23.—Skin collagen from a premature infant (birth weight, 1,030 g.). Preparation incubated with collagenase for 3 hrs. Back ground network of tiny tactoids and beaded fibrils. × 15,600.

process these ribbons disintegrated into granular debris and "beads".

Fig. 24.—Skin collagen from a 24-year-old patient with subacute bacterial endocarditis. Preparation incubated with collagenase for 24 hr shows three structures in the same field: striated collagen, a "granular degenerating" fibre, and a "moth-eaten" fibre. × 18,400.

(4) *Beaded Fibrils and "Beads"*.—Numerous small, spherical, dense structures termed "beads" were observed either lying separately or linked together to form beaded fibrils. The "beads" measured about 250 Å in diameter, whereas the beaded fibril axial periodicity varied from 455-610 Å, according as the component beads were widely spaced or close together. Their numbers were directly proportional to length of incubation, and at 24 hrs "granular degenerating" and "moth-

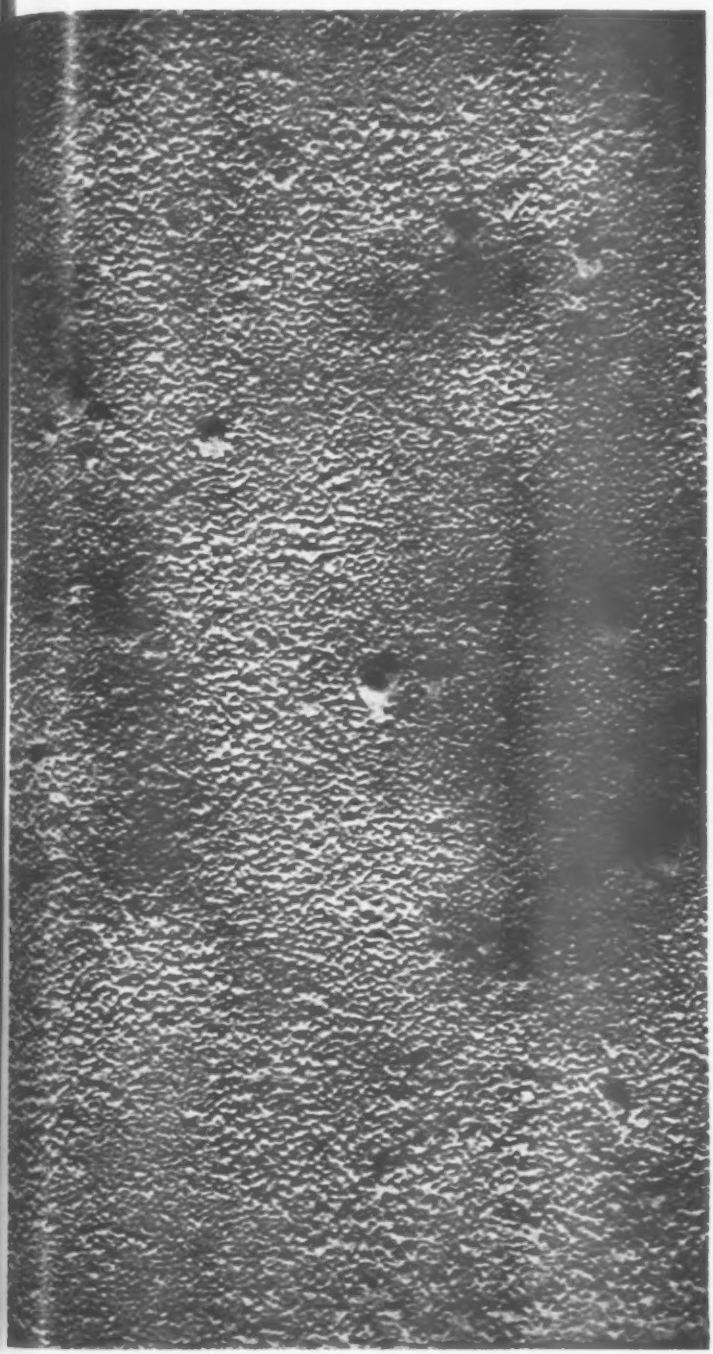


Fig. 25.—Skin collagen from a 27-year-old patient dying of acute pancreatitis. Preparation incubated with collagenase for 24 hrs, shows masses of "beads", about 250 Å in diameter. × 35,000.

eaten" fibres were seen disintegrating into "clouds" of "beads" (Figs 13, 14, 21, and 25). In some areas the beaded fibrils were "lined-up in register" to form skeleton fibres (Fig. 20).

Fig. 26 (overleaf) shows the proportion of these various forms of collagen at different incubation times in the different age groups. The axillary (non-abdominal) skin of one patient with dermatomyositis and of two others aged 51 and 52 years who gave atypical results were excluded (see Table). Collagen from one infant examined at 2 and 7 min. showed fibre-change too scanty to be useful. 6-hr incubations were examined in eight cases and all except one presented practically the same picture as that seen at 3 hrs. The exception was the collagen from the 52-year-old patient with carcinoma of lung (noted in the Table) which digested excessively for his age.

All the seven cases of erythroblastosis foetalis looked exactly the same, both macroscopically and microscopically, at any given time. Collagen showing "standard" collagenase change was not seen after the 10-min. examination, and moth-eaten fibres were absent throughout, except in one case at 24 hrs. Each of the five newborn infants presented identical microscopic pictures at any given time, but they all differed from those with erythroblastosis in having more collagen showing the standard change at both the 10-min. and the 3-hr incubations. This difference could be related to age; the erythroblastotics were mostly premature deliveries. The 1- to 6-month group showed a similar picture, except for a smaller amount of "granular degenerating" fibres at 3 hrs. Thus the predominant feature of the sixteen individuals aged 0-6 months was the early absence of striated collagen showing the standard enzyme change, the fields being filled with masses of granular degenerating fibres, numerous, long-beaded fibrils, and "clouds" of beads. "Moth-eaten" fibres were not seen, except in one case at 24 hrs.

In specimens from patients over 2 years old the bundles of striated collagen were noted to be larger and more "compact" at 3 hrs, while moth-eaten fibres figured prominently from 1 to 24 hrs. Granular

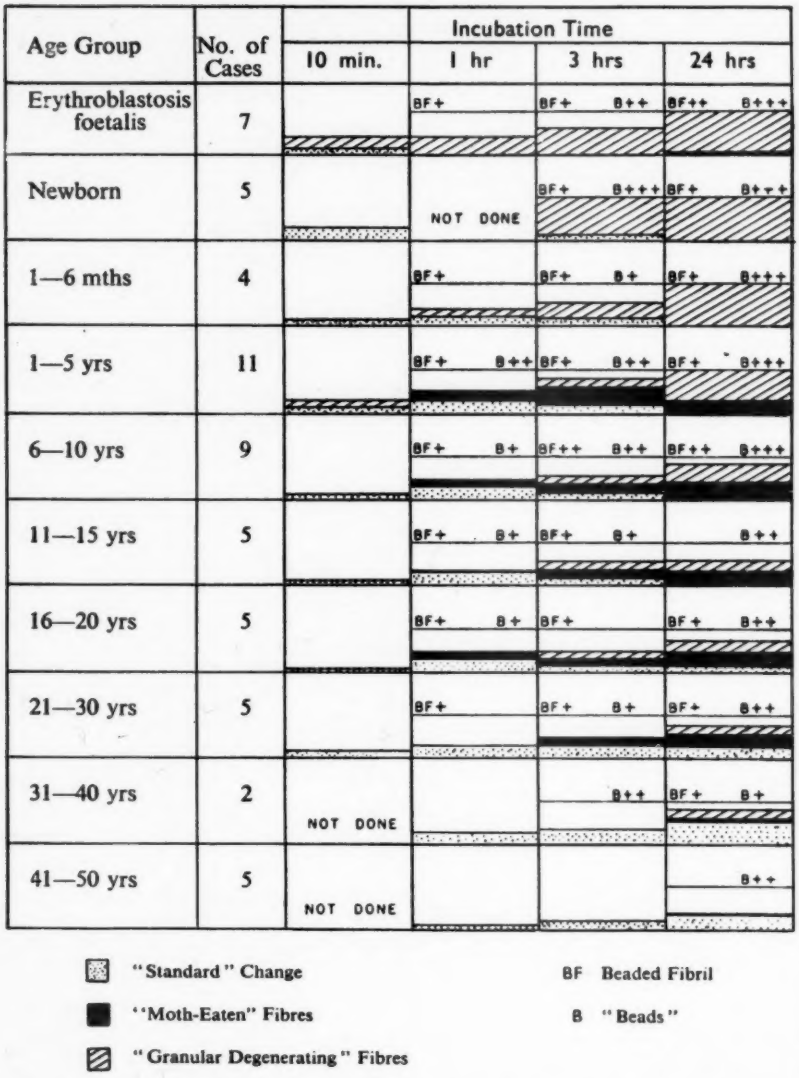


Fig 26. Analysis of the abdominal skin collagen from 58 cases with and without "collagen disease" during incubation with collagenase at 37C°

elements did not appear until after 3 hrs incubation. Many beaded fibrils and beads were seen at 1 hr, the number of beads increasing with the length of incubation.

Analysis of the first two decades revealed a progressive diminution of granular degenerating fibres with a corresponding decrease in the number of "beads". Moth-eaten fibres still figured prominently and a fair amount of striated collagen showing "standard" change remained at 3 hrs. At 24 hrs this standard change was absent in cases under the age of 15, but above this age it was seen more and more often, so that in cases over 30 years old it was the predominant finding. The collagen from individuals in the third and fourth decades contained a diminishing number of moth-eaten fibres and granular elements, until, over the age of 40, only relatively small quantities of striated collagen showing standard change were seen, with scanty moth-eaten fibres and some beads at 24 hrs.

Thus the striated collagen showing "standard" collagenase change was seen only during early incubation in babies and young children; after 3 hrs the fields contained masses of granular, and disintegrating granular degenerating fibres accompanied by numerous beaded fibrils and "beads". In adults the striated collagen was seen at all incubation times, dominating the picture over the age of 30. "Granular degenerating" fibres were present at 10 min. in the erythroblastotics, but did not appear until 3 hrs incubation in patients over 5 years old, and not until 24 hrs in patients over 20 years old; in patients over 40 they were completely absent. "Moth-eaten" fibres figured prominently between the ages of 1 and 20, but during the third to fifth decades their numbers steadily decreased.

The youngest individual examined was a 6- to 7-month gestation premature infant, weighing 1,030 g. A profuse background network of tiny tactoids and long beaded fibrils was present in all material prepared from tubes incubated for 3 and 24 hrs (Fig. 23). This was far more pronounced than in two older premature infants and in the full-term babies examined, where, although scattered beaded fibrils and beads were numerous, they were insufficient to form a background network. The eight cases that did not digest (Table) showed only very scanty striated collagen throughout incubation, which was either unaltered or underwent "standard" collagenase change; four presented occasional moth-eaten fibres and a few beads at 24 hrs, but granular elements were entirely absent. The two cases exhibiting excessive macroscopic digestion for their age (Table) showed an electron microscopic picture

throughout incubation comparable to that of a child under 5 years old.

Cases of Collagen Disease.—The three cases of collagen disease that did not digest (Table) had very scanty striated collagen throughout, either unaltered or showing "standard" change. The microscopic picture of the three cases of rheumatic heart disease conformed with that from the other members of their respective age groups. One patient with polyarteritis nodosa (aged 11 years) and two with disseminated lupus erythematosus (aged 12 and 19 years) showed less than the average breakdown for their respective age groups at the various incubation times.

II. Untreated Collagen

The majority of skin samples, representing all age groups and a variety of diseases, showed the usual picture of homogenized collagen as described above (Fig. 2). However, five showed collagen fibrils composed of short lengths tapered at both ends (tactoids) dove-tailed together to make a uniform fibril (Figs 27-31). Where the two ends dove-tailed, the axial repeating period of each component remained in register. Some of the fibres appeared flattened and surrounded by finely-beaded material composed of particles of uniform size, which were easily distinguishable from the background grain (Fig. 31). Others presented a rope-like appearance (Figs 27-29). Measurement of 42 tactoids indicated a basic unit of 6,000-9,000 Å in length, the longer tactoids being twice, three, and four times this size.

The five cases showing the above changes were four newborn infants dying from erythroblastosis foetalis and a bed-ridden 9-year-old child with congenital hydrocephalus, marked emaciation, spasticity of all extremities, multiple decubiti ulcers, terminal pneumonia, and a mental age of 3 years. The remaining skin samples presented the usual appearance of unaltered collagen after homogenization, *i.e.* long, striated fibrils with square or torn ends cut by the blendor and an occasional tapered end.

Discussion

I. Incubated Controls and Collagen Incubated with Collagenase

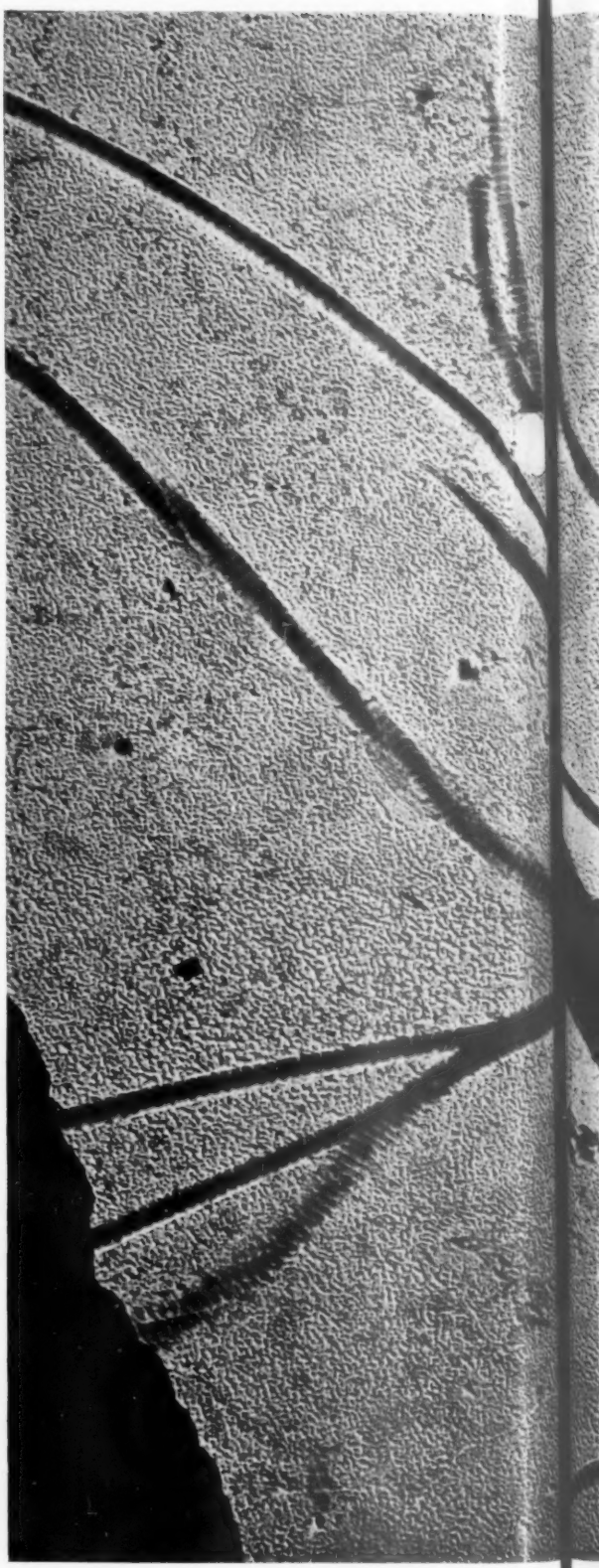
(A) **Macroscopic Digestion.**—The significant difference between collagen digestion in babies and young children and in adults (Fig. 3) was previously noted from the chemical standpoint (Keech, 1954a). Collagen from infants produced nearly twice as much, and from children aged 1 to 10, half again as much soluble nitrogen in a given time as adults over the age of thirty. But these readings were taken at 3 hrs for the reasons stated (Keech, 1954a), whereas in the present study incubation was extended to 24 hrs. The fact that at 24 hrs the digestion in individuals below the age of 40 was $3\frac{1}{2}$ times greater than that found above this age may indicate a relative insusceptibility to collagenase in the older age group.

The reason for the lack of digestion in eight patients aged 1 to 52 years (Table) remains obscure. All the collagen samples were satisfactory and well extracted. Therapy cannot be incriminated. Collagen from seven other children with acute leukaemia and receiving the same multiple treatments (blood transfusion, antibiotics, A-methopterin, cortisone, and ACTH) digested normally for their age group. The cases of dermatomyositis and juvenile rheumatoid arthritis had received heavy doses of the steroid hormones, but so also had other individuals who conformed to the general response-pattern. In fact, the patient with fulminating rheumatic carditis who exhibited excessive collagen digestion (Table) had received large doses of cortisone for 12 days before death.

Some of the unused extracted collagen samples prepared for the chemical study already mentioned (Keech, 1954a) were used for this investigation, and the same exceptions in collagen disappearance were noted, *e.g.* the lack of digestion associated with negligible nitrogen recovery in the 5-year-old child with dermatomyositis and in the 13-year-old child with rheumatoid arthritis. The excessive collagen digestion of the 52-year-old patient with carcinoma of the lung was again seen; it may or may not be related to his terminal treatment with intravenous nitrogen mustard. The absence of digestion of collagen in rash-bearing skin and the normal digestion in abdominal skin from the other case of dermatomyositis in a 9-year-old child is unexplained.

(B) Electron Microscopic Findings.—Gross (1953) pointed out that electron microscopy has its limitations as a method of studying collagen in that it relies for identification on the characteristic morphological "fingerprint" of axial periodicity. He produced a wide variation in structure by a few known agents, and concluded that:

> a systematic stepwise investigation of controlled alterations, progressing from purified components to systems of increasing complexity, will not only lead to a better understanding of the chemistry involved in physiological and pathological processes but may give more specific meaning to the observed histological changes.



He noted that:

> in several preparations of intact human skin, rat-tail tendon, and purified cow-hide that had been digested with collagenase, moderate numbers of long filaments resembling strings of beads with very regular periodicity of about 600-650 Å.

He was unable to determine their origin. Similar beaded fibrils were also found by Gross (Matoltsy and others, 1951) in the vitreous humour of cattle eyes following fragmentation in a Waring blendor for 5-10 min. at 0-5° C. The axial periodicity varied between 500-850 Å, averaging 610 Å. No enzyme was used.

From the extensive observations made in the present study on purified collagen from all age groups, it is very difficult to escape the conclusion that both the beaded fibrils and "beads" are the smallest visible breakdown products of collagen. Fig. 26 shows that these fibrils occur after 1 to 24 hrs' incubation, but only after 24 hrs over the age of 30. In the presence of striated collagen these fibrils would always "fit in" with the axial periodicity of the larger fibril had they been aligned beside it (Fig. 21). The component "beads", however, are the most constant and numerous end-product. It is believed that they represent the smallest collagen macromolecule that it is now possible to photograph, although more powerful instruments may visualize even smaller particles in the future.

Recent work by Watson, Rothbard, and Vanamee (1954) demonstrated re-precipitation of rat tendon collagen in fibrous form when normal rabbit serum was added to the acetic acid collagen solution. However, when the solvated collagen was added to homologous antiserum a globular precipitate occurred. The authors interpret this as representing the macromolecules of collagen coated with antibody, the antibody preventing fibre formation. Their electron micrographs illustrate clumps of ill-defined, globular material which may well be the same basic collagen component described in the present paper, the "beads" being the collagen macromolecules minus the antibody coating.

Wyckoff (1949) illustrated collagen fibres from animal Achilles tendon after immersion in weak acid solution. His Fig. IX, 31, 32, and 34 shows that these consist of:

> a bundle of filamentous macromolecules of exceedingly small cross-section . . . the cross-bands persist, however, in the remains of a ruptured fiber.

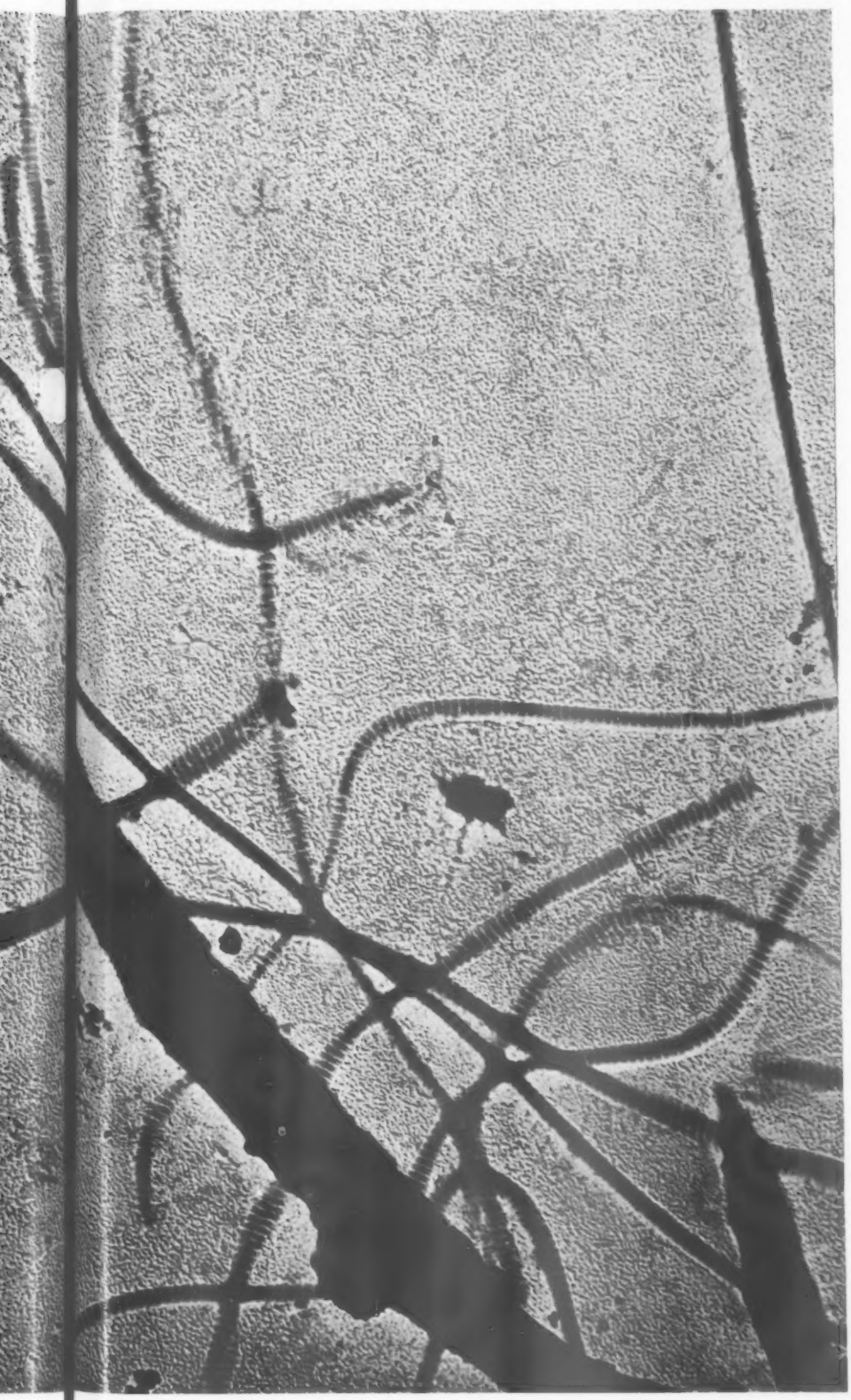


Fig. 27.—Untreated skin collagen from a 9-year-old child dying from hydrocephalus. Preparation fragmented in de-mineralized water in Waring blendor in the cold room. The fibrils are composed of short lengths of collagen tapered at both ends (tactoids), dove-tailed together to make a uniform structure. Where the two ends dove-tail, the axial-repeating period of each component remains in register. Some parts of the fibrils appear flattened and surrounded by a finely beaded material continuous with the substance of the fibril. × 18,500.

Fig. 28.—Untreated skin collagen from a newborn infant dying of erythroblastosis foetalis. Same description as for Fig. 1. The rope-like structures have a uniform, narrow palladium shadow surrounding each cigar-shaped component instead of a series of humps. This is believed to indicate a separation of fibril tactoids and not a true twisting (compare Fig. 2*a*). × 19,000.

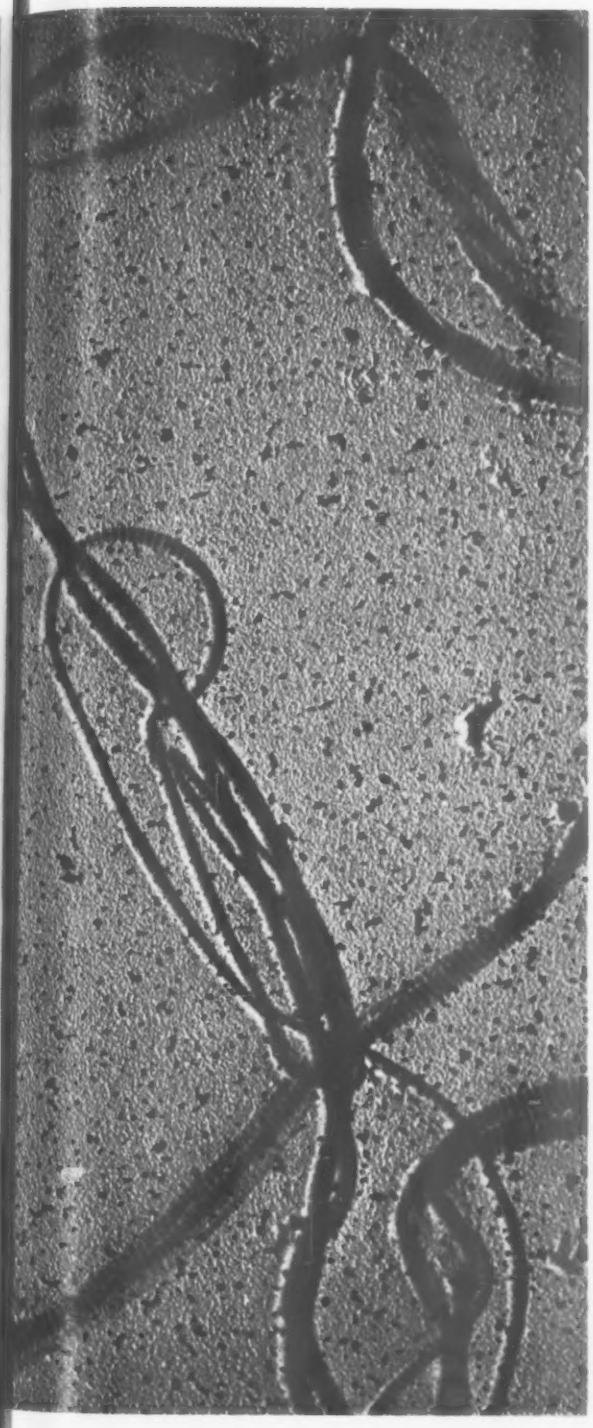


Fig. 29.—Same as Fig. 28. × 16.000.

Fig. 30.—Untreated skin collagen from another newborn infant dying of erythroblastosis foetalis showing multiple dove-tailing. × 18,500.

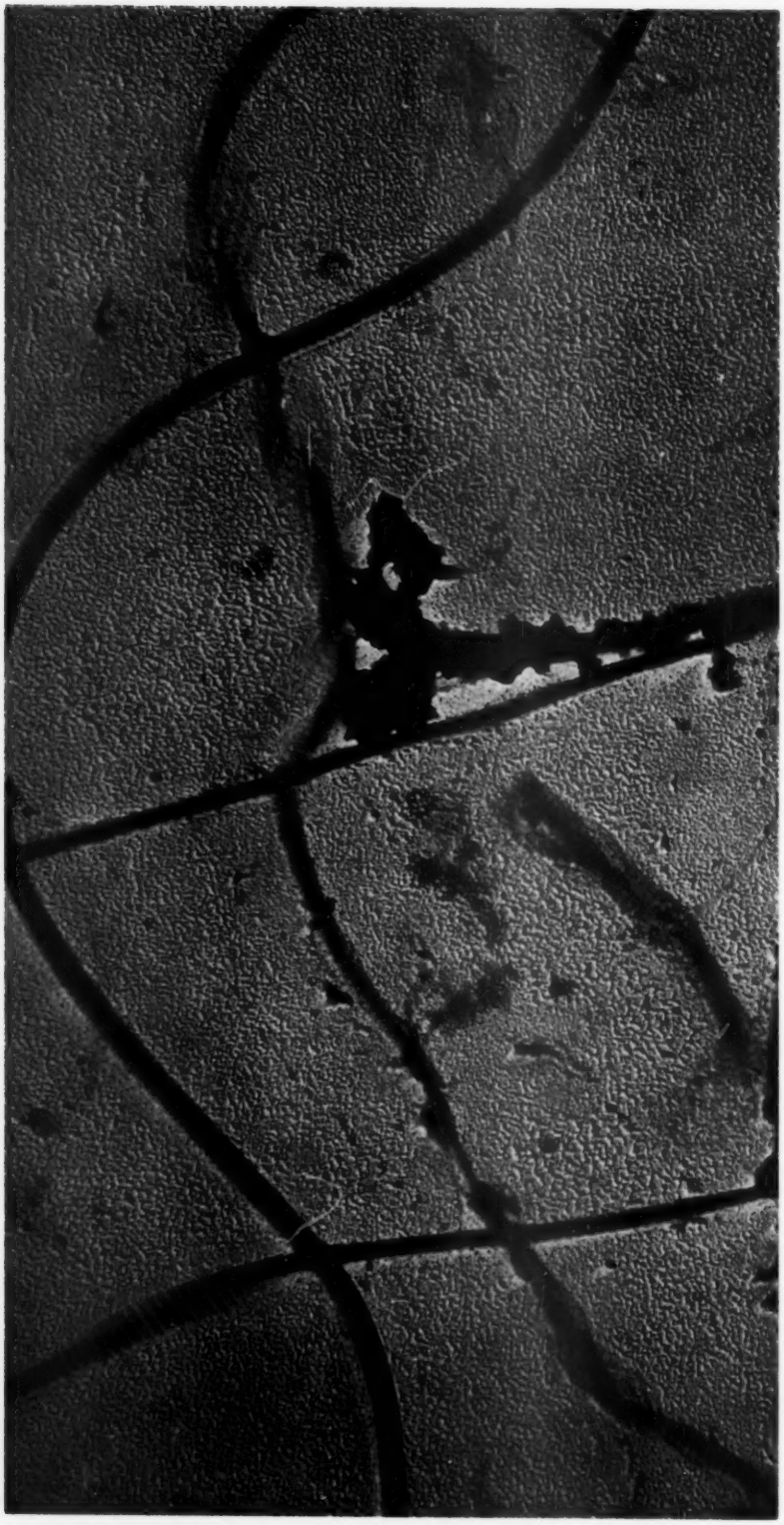


Fig. 31.—Untreated skin collagen from a 9-year-old child dying from hydrocephalus. Same description as for Fig. 27. The continuity of the finely beaded material with the fibril substance is well shown. × 18,500.

These filaments are aligned longitudinally and strongly resemble the beaded fibrils described above.

Gross (1953) illustrated the effect of 0·1 *N* HCl on cow-hide corium collagen. His Fig. 4 shows swollen, flattened degenerated fibres after immersion for 3 hrs at room temperature, rather resembling the "granular degenerating" fibres described in the present study. Vanamee and Porter (1951, Fig. 2) illustrate somewhat similar structures obtained by partially dissolving rat-tail tendon with acetic acid. However, both these occurred in an acid solution, whereas the break-down products described in the present investigation were formed in a solution buffered at *p*H 7·3, this *p*H being unchanged after incubation.

Rich and others (1953) described altered collagen fibrils from local anaphylactic lesions in rabbit skin, and correlated the histological and electron microscopical appearances. Affected fibrils showed loss of axial periodicity, hyaline transformation, variation in density, irregularities of the margins, and evidences of swelling and fragmentation. Even though the descriptions and illustrations do not resemble the collagenase break-down products discussed in the present work, it is considered important to mention that structures bearing no resemblance to the usual striated collagen have been convincingly demonstrated as stemming from this source.

It is hoped that the above description of the effect of collagenase on known collagen substrates from different age groups may help in defining altered collagen in pathological tissue where the characteristic morphological "finger-print" of periodicity may be lost.

II. Untreated Collagen

Gross (1953) illustrated similar structures after immersion of purified (extracted) cow-hide corium collagen fibrils in 0·1 *N* HCl at room temperature for a few minutes. Within 10 min. many fibrils were flattened and distorted along their length. After several hours there was general disintegration of axial structure with marked swelling and flattening along the whole length of most of the fibrils. As described above, the material under discussion in this investigation was simply unfixed human abdominal skin collagen homogenized in de-mineralized distilled water in the cold room and kept well below body temperature. No extraction had been performed and no chemical or enzyme added. Gross (1953) stated that excessive blending might cause fragmentation resembling that illustrated in his Fig. 2, but, in the present study, all 61 skin samples were blended for the same length of time (15 min.) and these changes were only noted in five cases. The majority of the rope-like fibres seen (Figs 27-29) were *not* considered to be twisted, as evidenced by the shape of the palladium shadow. Instead of a series of "humps", each cigar-shaped component was outlined by a narrow shadow quite unlike that cast by the rope-like re-precipitated collagen illustrated by Noda and Wyckoff (1951) and by Wyckoff (1952). This was taken to indicate a *separation* of fibril tactoid components and *not* a true twisting. The latter is illustrated in Fig. 2(*a*).

Erythroblastosis foetalis is a common cause of foetal maceration, but the skin used was macroscopically normal with no evidence of autolysis. However, it is possible that such a generalized antigen-antibody disturbance continued throughout gestation could render the collagen less stable and more susceptible to disintegration by the mechanical action of blending. Coons and others (1951) and Kaplan and others (1950) demonstrated the presence of a large amount of antigen-antibody precipitate on dermal collagen after intravenous injection of various fluorescein-labelled antibodies into mice. Pneumococcal polysaccharides showed a remarkable persistence on collagenous fibres, and the connective tissue of the dermis following injection of egg albumin, bovine albumin, and human γ-globulin was so brilliantly fluorescent that the dermal cells were obscured. The authors state:

> It would appear that the antigen present in the tissue fluids had become adsorbed on to the collagenous fibers. The epithelial cells of the epidermis and hair follicles were negative. The human γ-globulin persisted six times as long as the two albumins.

Another possible explanation should be mentioned. The heat generated during homogenization may have affected the unstable erythroblastotic collagen, as electromicrographs of heat-treated collagen show a somewhat similar picture (Reed and Wood, 1954). Although the temperature of the suspension at the end of blending was always well below body temperature, the temperature at each particle-fluid interface may have been higher. Or the damaged erythroblastotic collagen may have become altered at a lower temperature than the stable substrate from the other individuals.

The findings described above suggest that at least some collagen fibrils may be composed of tactoids, the tapered ends being closely dove-tailed and, under normal conditions, invisible. On partial solution with dilute HCl (Gross, 1953), after digestion with collagenase (Gross, 1953; Keech, 1954b) in re-precipitated collagen (Vanamee and Porter, 1951), or in rare instances after mechanical blending, these bi-tapered building blocks are revealed.

Hypothetical Structure of Collagen.—This dove-tailing (Figs 27-31) suggests that collagen fibrils are composed of a chain of tactoids, the dove-tailed sections possibly providing weak points for enzyme separation. In fact, Fig. 7 suggests a localized through-the-bundle point of action by collagenase. The cigar-shaped macro-fibrils occurring in fibrous proteins and consisting of dove-tailed microfibrils is discussed by Keech (1954b). The flattened fibril areas shown in Figs 27-31 are surrounded with finely-beaded material. Careful examination suggests that this material is composed of beaded fibrils which maintain continuity with the parent fibril, rather like the effect produced by weak acid illustrated by Wyckoff (1949, Fig. IX, 32). As described above, collagenase breakdown produces beaded fibrils with a periodicity equivalent to that of their parent fibres (Fig. 21). Fig. 20 reveals that these beaded fibrils are aligned longitudinally with the competent beads in register. Fig. 32 (overleaf) illustrates a hypothetical intra-tactoid structure compatible with these findings.

Summary

The effect of collagenase on extracted human abdominal skin collagen from sixty individuals of all ages, dying from a variety of causes, was studied under the electron microscope. Three different types of breakdown structure were found, each ultimately disintegrating to the same end product, or "bead", believed to be the smallest collagen component yet demonstrated.

The proportion of these three elements varied

Fig. 32(*a*).—Skin collagen from a 28-year-old patient dying from a coronary thrombosis. Preparation incubated with collagenase for 1 hr. Fibres composed of many dove-tailed tactoids. × 15,300

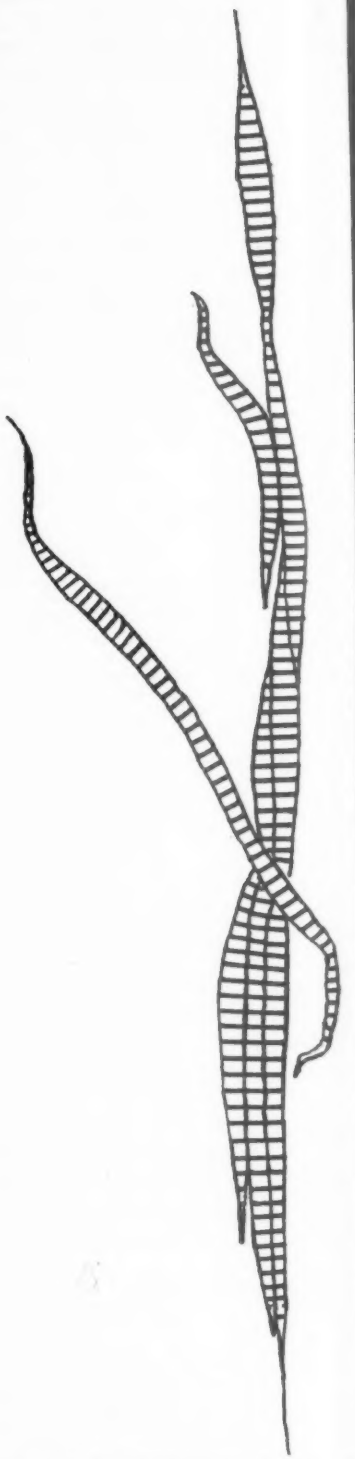


Fig. 32(*b*).—Diagrammatic drawing of area marked with arrows in (*a*) to show dove-tailing.

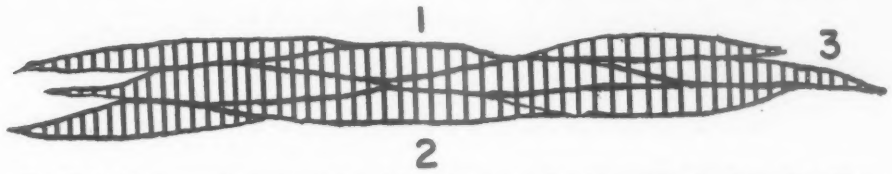


Fig. 32(*c*).—Diagrammatic representation of fibre structure as found in untreated collagen (Figs 27-31).

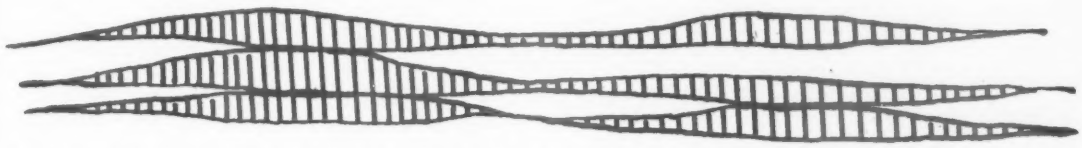


Fig. 32(*d*).—Same fibre bundle as shown in (*c*) after hypothetical enzyme action. The individual tactoids have become elongated. If the components marked 1, 2, and 3 in (*c*) are removed in the process, localized through-the-bundle fibre narrowings result as illustrated in Fig. 7.

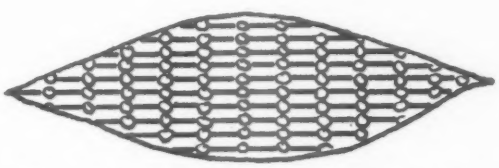


Fig. 32(*e*).—Hypothetical intra-tactoid structure. This longitudinal arrangement of beaded fibrils in register is supported by:
(*i*) the skeleton fibre illustrated in Fig. 20;
(*ii*) the fact that in the presence of striated collagen, the beaded fibrils would always "fit in" longitudinally with the axial periodicity of the larger fibril had they been aligned beside it (Fig. 21);
(*iii*) the flattened fibril areas shown in Figs 27-31. Careful examination of the surrounding finely-beaded material suggests that it is composed of beaded fibrils which maintain continuity with the parent fibril.

markedly with age and length of enzyme-incubation. At any given time there was a characteristic picture for different age groups. No definite correlation could be established between different diseases or treatments.

A significant difference was found in macroscopic digestion between different age groups, collagen from babies and children disappearing more rapidly than that from adults. The 3-hr digestions showed a steady decline with increase in age, and the 24-hr digestions from patients under the age of 40 were $3\frac{1}{2}$ times greater than those from individuals in the fifth decade.

Collagen digestion did not occur in eight cases. This is so far unexplained.

The untreated skin of non-incubated controls showed changes suggesting that at least some collagen fibrils have a multiple-tactoid structure.

In pathological tissue, collagen may be so altered as to pass unrecognized. It is hoped that this paper, by describing the effects of collagenase on known substrates from different age groups, may serve as a line of reference in attempts to define altered collagen in pathological tissue, when the characteristic morphological "finger-print" of axial periodicity may have been lost.

I am very grateful to the late Dr. Henry Bunting and to Drs. W. G. Banfield and W. H. Gaylord for constructive criticism and guidance in this work. I am indebted to Dr. A. A. Liebow and the staff of the Pathology Department at the Grace-New Haven Community Hospital, and to Dr. C. S. Petty at The Children's Medical Centre, Boston, for autopsy material. I also wish to thank Dr. J. D. MacLennan for the collagenase, and Dr. J. R. Paul in whose department this work was done.

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Collagène de la peau humaine de différents groupes d'âge avant et après la digestion par la collagénase Etude au microscope électronique

RÉSUMÉ

On a étudié au microscope électronique l'effet de la collagénase sur le collagène extrait de la peau abdominale de soixante sujets de tout âge morts de causes variées. On a trouvé trois types différents d'écroulement de la structure, tous aboutissant à la formation d'un seul produit de désintégration finale, la "perle", le plus petit composant connu du collagène.

La proportion de ces trois éléments variait considérablement selon l'âge et le temps d'incubation enzymatique. A un temps donné on voyait un tableau caractéristique pour un groupe déterminé d'âge. Il n'a pas été possible de définir un rapport avec une maladie ou un traitement quelconque.

On a trouvé une différence significative dans la digestion macroscopique selon l'âge: le collagène des nourrisons et des enfants disparaissait plus rapidement que celui des adultes. La digestion de 3 heures diminuait régulièrement avec l'avance de l'âge et la digestion de 24 heures pour les sujets de moins de 40 ans était 3½ fois plus prononcée que celle pour les sujets âgés de 40 à 50 ans.

La digestion du collagène ne s'est pas produite dans huit cas. Pour le moment on ne peut pas expliquer ce phénomène.

La peau qui n'a pas été traitée ni incubée présentait des altérations suggérant que tout au moins certaines fibrilles collagènes ont une structure tactoïde multiple.

Dans le tissu pathologique le collagène peut être si altéré qu'il devient méconnaissable. On espère que cet article, qui decrit les effets de la collagénase sur des extraits déterminés provenant de sujets d'âge différent, offre des critères permettant de définir le collagène altéré dans un tissu pathologique quand l'"empreinte digitale" morphologique et caractéristique de la périodicité axiale se perd.

Colageno de la piel humana de diferentes grupos de edad antes y después de la digestión por la colagenasa Estudio al microscopio electrónico

SUMARIO

Se estudió al microscopio electrónico el efecto de la colagenasa sobre el colageno extraido de la piel abdominal de sesenta individuos de todas edades, muertos de causas variadas. Encontráronse tres tipos diferentes de desintegración de la estructura, acabando todos con formar un solo producto final, "la cuenta de rosario", el más pequeño componente de colageno que se conozca.

La proporción de estos tres elementos fué muy variable según la edad y el tiempo de incubación enzimática. En tiempos determinados se pudo ver el cuadro característico para cada grupo de edad. No se pudo definir correlación alguna con varias enfermedades o tratamientos.

Encontráronse diferencias significativas en la digestión macroscópica entre varios grupos de edad, el colageno de los infantes y niños desapareciendo más pronto que el de los adultos. La digestión de 3 horas bajaba uniformemente con el avance de la edad y la digestión de 24 horas para los sujetos de menos de 40 años fué tres veces y medio superior a la para los sujetos en la quinta decena de vida.

La digestión del colageno no se produjo en ocho casos; fenómeno que no se puede explicar todavía.

La piel que no fué tratada ni incubada presentó alteraciones sugeriendo que por lo menos ciertas fibrillas colagenas tienen una estructura tactoide multiple.

En el tejido patológico el colageno puede sufrir alteraciones a punto de pasar inadvertido. Se espera que este artículo, al describir los efectos de la colagenasa sobre extractos determinados procedentes de sujetos de edad diferente, sirva de criterio para definir el colageno alterado en un tejido patológico en caso de perderse la "huella digital" morfológica, característica de la periodicidad axil.

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RHEUMATOID ARTHRITIS: DYE RETENTION STUDIES AND COMPARISON OF DYE AND RADIOACTIVELY LABELLED RED CELL METHODS FOR MEASUREMENT OF BLOOD VOLUME*

BY

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The congo red test for amyloidosis (Bennhold, 1923) measures the proportion of this dye which is retained in the plasma one hour after its intravenous injection. In our previous experience, 45 normal subjects retained 70 per cent. or more, and five patients with histologically proven amyloidosis retained 50 per cent. or less, usually much less, in this period. This is in accord with other reports (Bennhold, 1923; Friedman and Auerbach, 1935; Taran and Eckstein, 1942; Lipstein, 1938; Stemmerman and Auerbach, 1944; Harmon and Kernwein, 1942; Pearlman, 1940; Unger and others, 1948). However, in 114 out of 227 patients with rheumatoid arthritis, we found values between 50 and 70 per cent. These intermediate values point to a difference in the fate of intravenously injected dyes in patients with rheumatoid arthritis as compared with normals. Estimates of blood volume in this disease based upon dye methods may therefore not be accurate. The availability of the radioactive sodium chromate-^{51}Cr method (Sterling and Gray, 1950) enabled us to measure the blood volume of a series of such patients simultaneously by two methods, one of which did not depend on a dye. In addition, we have compared the one-hour retention of congo red with that of Evans' blue in another series of patients. These results and other observations relevant to these problems are herein reported.

Methods

Red cell masses were measured by the method of Sterling and Gray (1950) which utilizes the affinity of sodium chromate for haemoglobin. About 35 ml. of the subject's blood was drawn, under sterile precautions, into a syringe containing 0·25 ml. 10 per cent. (weight for volume) heparin solution, and centrifuged (30 min., 2,700 r.p.m., 15 cm. radius); the plasma was removed and the red cells gently mixed for one hour at room temperature with about 15 ml. normal saline containing approximately 1·5 mg. sodium chromate-^{51}Cr with radioactivity of about 100 microcuries. The cells were then separated from the saline supernatant by centrifugation, and washed three times with fresh saline. After two such washings, the radioactivity of the supernatant became constant at approximately 1 per cent. The cells were then stored overnight at 4° C. Before using they were resuspended in the original plasma (filtered through sterile gauze if any fibrin clot had formed overnight) and thoroughly mixed by continuously inverting the tube for 3 min. A sample was removed for determination of radioactivity and haematocrit; the rest of the tagged blood being used for injection.

Plasma volumes were measured by a modification of the Evans' blue method of Gibson and Evans (1937) and by a modification of the congo red method of Rowntree, Brown, and Roth (1929). A 0·1 per cent. solution of Evans' blue was prepared in sterile ampoules. Two batches of dye were used; each was standardized separately according to the method of Gibson and Evelyn (1938) and checked against the other. Similarly, a 1 per cent. congo red solution was prepared and a single batch of ampoules were standardized by dilution in a 10 per cent. solution of serum in saline. Tagged cells or dye were injected, using syringes calibrated by weight. Blood was drawn from one anticubital vein for blank values of dye concentration or radioactivity, the needle left *in situ*, and the syringe containing dye or tagged cells substituted. Blood was taken from the opposite vein at 4, 10, 30, and 60 min. through a No. 19 needle with the tourniquet left on for about 15 seconds. Dye concentrations were measured against the pre-injection blank in a Junior Colman spectrophotometer, using serum or heparinized plasma. In one patient in whom both

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plasma and serum were used the results were identical. Optical density of the plasma at 625μ and 540μ (Evans' blue) and at 510 (congo red) were plotted on semilog paper against time. A few haemolysed samples, showing unexpectedly high absorbtion at 540μ, were rejected. Almost all values lay on a straight line, showing that the loss of both dyes from the blood stream was exponential. This straight line was retropolated (as recommended by Gregersen and Schiro, 1938), and the optical density at zero time was used for calculating plasma volume (P.V.) according to the formula:

$$\text{P.V.} = K \times \frac{\text{Amount of dye injected (mg.)}}{\text{Optical density at zero time}} \quad . \; . \; . \; . \; (1)$$

where K is the ratio of optical density to the concentration of the dye as determined by the slope of the calibration curve.

Plasma retentions of dye were calculated from the equation:

$$\text{Retention} = \frac{\text{Optical density at zero time}}{\text{Optical density at 60 minutes}} \times 100 \; . \; . \; . \; (2)$$

using values for optical density derived from the graph. This is not quite the same as the standard method, which compares the observed 60-min. and 4-min. values. When measuring red cell mass (R.C.M.), the radioactivity of 1·0 ml. aliquots of tagged blood and of the 30- and 60-min. samples were compared in a scintillation counter (after correcting for background and for radioactivity of the respective plasmas) according to the formula:

$$\text{R.C.M.} = \frac{\text{Volume of tagged blood injected} \times \text{the haematocrit of the tagged blood} \times \text{counts per ml. of tagged red cells}}{\text{counts per ml. of red cells in sample.}}$$

The mean of the 30- and 60-min. results was taken.

Haematocrits were determined in duplicate in 2-ml. tubes with an internal diameter of 0·5 cm. by centrifuging for 30 min. at 2,700 r.p.m. with a 15-cm. radius, several different estimates being made on separate aspects of the tube. The mean of the 30- and 60-min. values was used, corrected by an arbitrary 97 per cent. to allow for trapped plasma. Total blood volume (Evans' blue or congo red methods) was calculated by dividing the plasma volume by the proportion of plasma in the corrected haematocrit. Total blood volume (^{51}Cr method) was calculated by dividing the red cell mass by the proportion of red cells in the corrected haematocrit. "True" total blood volume (independent of the haematocrit) is the sum of the plasma volume (Evans' blue) and the red cell mass (^{51}Cr). Surface area was computed according to the tables of Dubois (1927), as modified by Boothby and Sandiford (1929). Height was measured erect if the subject could stand straight, or in bed using a flexible tape measure where deformities were present. Sedimentation rates were measured by the method of Rourke and Ernstene (1930) and were corrected for haematocrit. Plasma proteins were separated and measured by the method of Gornall and others (1949). Results were analysed by standard statistical methods; differences likely to have arisen by chance in less than 5 per cent. of trials were considered significant.

Subjects

The subjects included eighteen women and seven men with peripheral rheumatoid arthritis, six men with rheumatoid spondylitis, one man with peripheral rheumatoid arthritis complicated by quiescent pulmonary tuberculosis and clinical amyloidosis, and ten women and one man who served as normal controls.

The patients had all shown characteristic changes of rheumatoid disease for more than 5 years, corresponding to Grades II and III severity of disease in the classification of the American Rheumatism Association (Steinbrocker and others, 1949), and at the time of this study had elevated sedimentation rates and no evidence of other disease including other causes of anaemia. In addition, all patients classified as suffering from peripheral rheumatoid arthritis had bilateral, clinical, and x-ray deformities of the hands, fingers, feet, and toes, amongst their other changes. All patients classified as suffering from rheumatoid spondylitis had clinical and x-ray changes in the spine and sacro-iliac joints. The patient with known amyloidosis and quiescent tuberculosis showed albuminuria and an enlarged spleen in addition to peripheral arthritis and pulmonary changes. All the arthritis subjects were hospital patients; their therapeutic regime included salicylates, rest in bed, and physiotherapy, but none was receiving specific haematinic treatment. The four patients who were receiving cortisone acetate will be discussed later. The normal subjects were members of the hospital staff or patients admitted for conditions unlikely to affect the blood volume. Tests were made in the morning with the subjects fasting. Apart from the patient with amyloidosis, none had a palpable spleen.

Results

(1) Comparison of the Evans' Blue and Congo Red Methods for Measurement of Blood Volume.—The Evans' blue and congo red methods were compared in 22 subjects: nine women and seven men with peripheral rheumatoid arthritis, five men with rheumatoid spondylitis, and one man with peripheral rheumatoid arthritis and amyloidosis. The tests were spaced at intervals of approximately one week, except in one man in whom they were applied simultaneously (see below). The results are shown in Table I (opposite).

Values for the Evans' blue tests have been arranged in order of increasing magnitude and with the exception of the patient with amyloidosis, all fall within or slightly above the range of 2,261 to 2,721 ml./sq. m., which is the range found in a series of normal female subjects to be discussed later, and is consistent with other reported normal ranges for this method. On the other hand, the total blood volume as measured by the congo red method gave unexpectedly variable values, which, although in some cases approximately the same as those obtained by the Evans' blue method, in most cases were much higher (Table I). It was thought that some factor

TABLE I
COMPARISON OF TOTAL BLOOD VOLUMES PER UNIT SURFACE AREA (l./m.²) CALCULATED FROM DILUTION OF EVANS' BLUE WITH THOSE CALCULATED FROM DILUTION OF CONGO RED

Group		Subject No.	Blood Vol./m.²		Difference between (*a*) and (*b*)
Condition	Sex		Evans' Blue (*a*)	Congo Red (*b*)	
Peripheral Rheumatoid Arthritis	Female	1	2,370	5,230	2,860
		2	2,400	2,510	110
		3	2,420	2,880	460
		4	2,440	3,350	910
		5	2,450	3,180	730
		6	2,500	3,020	520
		7	2,610	2,700	90*
		8	2,730	2,580	−150
		9	3,130	3,100	−30*
	Male	10	2,410	3,180	770†
		11	2,560	2,590	30
		12	2,570	2,660	90
		13	2,690	3,180	490
		14	2,720	3,010	290
		15	2,870	3,260	390
		16	2,910	6,740	3,830
Spondylitis	Male	17	2,520	2,790	270
		18	2,670	3,180	510
		19	2,770	7,350	4,580*
		20	3,000	5,260	2,260
		21	3,140	3,170	30
Amyloidosis	Male	22	3,620	5,990	2,370

* Patients 7, 9, and 19 were receiving 50, 37·5, and 100 mg./day cortisone acetate orally respectively.
† In this patient both dye methods were used simultaneously.

in the blood of rheumatoid arthritis patients might cause the large variation in the apparent initial dilution of the congo red by interfering with the colour of the dye when mixed with plasma. This was tested by taking freshly-drawn heparinized plasma from twelve patients with typical rheumatoid arthritis of all grades of severity. Each sample was diluted to 10 per cent. with normal saline, to which congo red dye had been added to reach a final concentration of 1 mg. in 2,500 ml. The optical density of the dyed plasma was compared with that of the same plasma diluted with saline only. Despite variation in the icteric index and hydrogen ion concentration of the plasma samples, the optical density of the dye was almost identical for all twelve.

(2) Plasma Retention of Congo Red and Evans' Blue in Rheumatoid Arthritis.—The amount of dye retained at the end of one hour was compared for both dyes for the same series of patients, excluding the patient with clinical amyloidosis. The mean retention of Evans' blue after one hour was 86·1 ± S.D. 1·2 per cent. The mean retention of congo red after one hour was 55 ± S.D. 10·2 per cent. The means are significantly different.

The following pairs of variables were examined and no significant correlation found:

A against B, C, D, E, G, H, and I
B against C, D, E, G, H, and I
C against F

A = rate of loss of Evans' blue from plasma.
B = rate of loss of congo red from plasma.
C = activity of disease as measured by sedimentation rate.
D = blood volume per sq. m. body surface as measured by Evans' blue method.
E = blood volume per sq. m. body surface as measured by congo red method.
F = discrepancy between two methods for measuring blood volume per sq. m.
G = plasma protein concentration.
H = plasma albumin concentration.
I = plasma globulin concentration.

Thus the tendency of congo red to leave the vascular system of some patients at a rapid rate is not explained in terms of association with any one of these other variables. Conversely, there is no evidence that this tendency in any way affects the Evans' blue method for measuring blood volume in this disease.

The patient with amyloidosis lost congo red from his plasma at a rapid rate, *i.e.* a half-disappearance time of 4 min., compared with about 65 min. for uncomplicated rheumatoid arthritis, and no dye was detectable in his plasma after 30 min. The same patient showed a fairly high one-hour retention of Evans' blue in his plasma, but the four values for optical density of this patient's plasma did not fall on a straight line when plotted on semilog paper against time. The curve indicated a rapid initial rate of loss of dye followed by a slower rate of loss after 10 min., as noted by Unger and others (1948).

In a man aged 29 who had peripheral rheumatoid arthritis with knee effusions, the two dyes were injected intravenously at the same time. Preliminary experiments *in vitro* had determined the small corrections needed for mutual interference of the dyes in the spectrophotometer. The one-hour plasma retention of congo red was 61 per cent., and that of Evans' blue was 92 per cent. Neither dye was detectable in the joint fluid after one hour. 24 hrs later, no congo red was detectable in the plasma, but a trace was found in the joint fluid; on the other hand 33 per cent. of the Evans' blue still remained in the plasma at this time, and its concentration in the joint fluid was approximately half that in the plasma.

In one other patient with a knee joint effusion, no Evans' blue dye was found in the synovial fluid at the end of one hour, though approximately one-tenth of the initial plasma concentration was found in both fluid and plasma on the following day.

(3) Repeatability of Congo Red Retention Test.—In two patients the congo red test was repeated after one week because the first test was technically unsatisfactory. Since congo red may be retained by amyloid-containing tissues for considerable periods of time after injection (2 months in a patient reported by Hass and Schulz, 1940), it has therefore been assumed by some that one congo red test will interfere with a second, presumably because the amyloid-containing tissues are saturated with the dye. This is not true for normal subjects (Rowntree and others,

1929), nor for the rheumatoid arthritis patients exemplified in Table II.

TABLE II

REPEATABILITY OF CONGO RED RETENTION TEST

Subject No.	Interval between Tests	Congo Red Retention %		Change per cent.
		1st Test	2nd Test	
1	2 hrs	76	84	+ 8
2	2 hrs	72	70	− 2
3	3 hrs	54	57	+ 3
4	1 day	46	62	+16
5	2 days	72	77	+ 5
6	3 days	48	50	+ 2
7	9 days	61	61	0
8	14 days	38	33	− 5
9	21 days	33	30	− 3
10	1 mth	32	39	+ 7
11	4 mths	60	63	+ 3

Average change = +3·1 (±5·6) per cent.

The following experiment done in this laboratory in 1946 is presented as further evidence against the possibility of "saturation" of the dye clearance mechanism.

A dilute solution of congo red in 5 per cent. dextrose solution was infused intravenously into one patient (who had peripheral rheumatoid arthritis without amyloidosis) on 3 days, giving a total of nine half-hour intervals, during which the infusion rate was kept approximately constant and observations on the plasma concentration of congo red were made (allowing at least 7 min. for equilibration). The total volume infused did not exceed 150 ml. in 2 hours and dilution effects have accordingly been disregarded. The results are tabulated in Table III.

TABLE III

CONGO RED BLOOD LEVELS ATTAINED AFTER 30-MIN. PERIODS OF INTRAVENOUS INFUSION AT A CONSTANT RATE

Day	½ hr Period	Rate of Congo Red Infusion (mg./min.)	Serum Level		Change per cent.
			After Initial Equilibration	At 30 min.	
1	1	1·03	0·083	0·068	−18
	2	1·13	0·068	0·073	+ 7
	3	1·18	0·073	0·069	− 6
	4	1·15	0·069	0·076	+10
4	1	0·64	0·100	0·081	−19
	2	0·64	0·081	0·070	−14
	3	0·99	0·069	0·071	+ 2
11	1	0·99	0·113	0·103	− 9
	2	2·75	0·122	0·134	+10

Thus, although there is variation from day to day as regards the plasma congo red concentration achieved by a given rate of infusion, there is no consistent increase between the start and end of each period, as might be expected if the congo red clearance mechanism becomes progressively "saturated".

(4) Comparison of Evans' Blue Retention in Normal and Arthritic Subjects.—A second series of subjects included ten women and two men with peripheral rheumatoid arthritis and ten normal women and one normal man who served as controls. The dye method being the same as previously used, the values for the one-hour retention of Evans' blue obtained in the normal subjects of this series can be compared with the arthritis patients in both series. For a uniform group of eighteen women with peripheral rheumatoid arthritis the mean dye retention was 87·7 ± S.D. 1·6 per cent. For nine normal women in the same age range the mean dye retention was 95·6 ± S.D. 1·6 per cent. The difference between the means (7·9 per cent.) exceeded twice its standard error (2·2 per cent.) and is significant. Two results (in one normal woman and in one patient) have been excluded from the calculation since in them the slope of the line from which the one-hour retention was calculated depended on only two points. These values are not materially altered if the results in all the arthritis subjects are compared with all the controls without exclusions for sex or completeness of data.

(5) Comparison of Evans' Blue and Tagged Red Cell (Sodium Chromate ^{51}Cr) Methods of Measuring Blood Volume in Patients and Controls.—Table IV (opposite) compares blood volume measured simultaneously by Evans' blue and tagged red cell methods in the same 23 subjects. The Evans' blue value is consistently greater than ^{51}Cr value, but the ratio $\frac{\text{Blood volume (tagged red cell method)}}{\text{Blood volume (Evans' blue method)}}$ is not significantly different for patients as compared with controls. Results for the three male subjects are given in Table IV, but are not included in the statistical comparison.

(6) Comparison of Red Cell Mass, Plasma Volume, and Total Blood Volume for Patients and Controls.—In this part of the study the figure for the total blood volume is the "true" blood volume, *i.e.* the sum of the plasma volume (Evans' blue) and the red cell mass (^{51}Cr). The comparison is limited to the ten women with arthritis and the ten control women of the second series. As would be expected, the women with arthritis were more anaemic than the controls (the venous haematocrit is given in Table V). The two groups did not differ significantly as regards age (Table IV). All the patients and eight out of ten of the controls were recumbent at the time of the test, but seven patients and two controls had been in bed for more than one week. Recumbency causes a slight increase in blood

TABLE IV

BLOOD VOLUMES IN TEN WOMEN AND TWO MEN WITH PERIPHERAL RHEUMATOID ARTHRITIS AND IN TEN NORMAL WOMEN AND ONE NORMAL MAN ESTIMATED SIMULTANEOUSLY BY THE EVANS' BLUE AND ^{51}CR METHODS

Sex	Subject No.	Age (yrs)	Body-Weight (kg.)	Surface Area (sq. m.)	Haematocrit (corrected) (per cent.)	Duration of Recumbency	Rheumatoid Arthritis: Duration (yrs)	Rheumatoid Arthritis: Sedimentation Rate (mm./min.)	Diagnosis of Normal Subjects	Total Blood Volume (ml.): Evans' Blue (ml.) (*a*)	Total Blood Volume (ml.): ^{51}Cr (ml.) (*b*)	Ratio (*a*)/(*b*)
	1	64	47·3	1·43	42·8	3 mths	5	1·29		4,130	3,360	0·81
	2	38	48·8	1·49	42·3	6 mths	13	1·51		3,890	3,430	0·88
	3	59	43·2	1·37	37·4	3 wks	10	0·68		3,520	3,200	0·91
	4	64	55·4	1·56	33·8	2 wks	15	1·25		4,410	3,620	0·82
	5	66	55·4	1·56	33·6	1 hr	8	1·08		4,440	4,170	0·94
	6	51	54·3	1·58	42·1	5 wks	6	1·27		3,670	3,430	0·93
	7	63	59·5	1·60	28·7	1 wk	15	1·35		4,380	4,270	0·97
	8	48	46·4	1·44	37·2	4 wks	15	1·34		4,490	3,330	0·74
	9	58	40·3	1·36	35·2	2 yrs	15	0·69		3,370	2,950	0·88
	10	52	56·4	1·58	39·6	3 wks	12	1·29		5,230	4,300	0·82
	Mean	56·3	50·7	1·497	36·255		10·4			4,153	3,604	0·871
	Standard Deviation	8·9	6·1	0·091	4·43					558	475	0·071
Female	11	64	60·5	1·65	41·9	2 hrs			Prurigo	4,490	3,850	0·86
	12	49	78·6	1·93	41·0	Ambulant			Normal	5,120	4,660	0·91
	13	37	52·9	1·37	42·4	5 hrs			Neurosis	4,100	3,480	0·85
	14	40	48·2	1·44	41·9	5 hrs			Neurosis	3,770	3,270	0·87
	15	41	45·4	1·39	40·5	3 days			Parotid tumour	3,650	3,140	0·86
	16	55	52·5	1·82	42·7	9 days			Mild diabetes	4,430	3,380	0·76
	17	76	68·6	1·83	41·8	2 wks			Cataract	4,140	3,790	0·92
	18	46	58·0	1·62	45·8	5 hrs			? Cholelithiasis	3,790	3,690	0·98
	19	43	63·5	1·63	40·1	3 days			Dermatitis of hands	3,800	3,590	0·94
	20	35	72·3	1·80	41·5	Ambulant			Dermatitis of hands	4,350	3,950	0·91
	Mean	48·6	62·0	1·668	41·95					4,164	3,680	0·885
	Standard Deviation	15·2	10·9	0·176	1·57					452	432	0·059
	Difference between Means	+7·7	**−11·3***	−0·171	**−5·699***					−10·6	−75·7	**−0·0141**
	S.E. of Difference	±5·6	**± 4·0***	**±0·0627***	**±1·488***					± 227	± 203	**±0·029**
Male	21	69	73·4	1·86	40·2	2 wks	5	0·67		5,280	4,750	0·90
	22	56	64·0	1·73	40·5	3 wks	6	1·57		6,200	4,400	0·71
	23	32	71·8	1·80	45·5	Ambulant			Normal	5,390	4,480	0·83

* Differences in bold type are significant.

volume (Thompson and others, 1928; Waterfield, 1931), but prolonged recumbency causes a decrease (Deitrick and others, 1948). The two groups differed significantly in body-weight (Line 1, Table V, overleaf).

Fig. 1 (overleaf) shows weight plotted against total blood volume per kg. Since there is a significant negative regression for this relationship (*i.e.* the lighter the subject the greater the blood volume per kg.), the greater total blood volume per kg., for the patients (Table V) might arise because the patients were lighter than the controls.

The two groups also differ significantly in their surface areas, but surface area plotted against blood volume per sq. m. shows no significant regression (Fig. 2, overleaf).

Surface area is therefore more likely to be a valid standard of reference for comparing the two groups. However, estimates of surface area depend on height, which was difficult to measure accurately in our deformed patients. The most satisfactory comparison is obtained by a statistical method which allows for difference in body-weight.

The relationship of blood volume to body-weight for all subjects is best represented by the mean regression line (Fig. 3, overleaf).*

Analysis of covariance compares the two groups on the basis of their variation about this line, and at the same time estimates the likelihood

* The finding that blood volume per kg. increases as body-weight decreases is illustrated by this regression line, which, if retropolated, has a positive value for blood volume at zero body-weight.

TABLE V

COMPARISON OF (*a*) PLASMA VOLUME (EVANS' BLUE), (*b*) RED CELL MASS (^{51}Cr) AND BLOOD VOLUME (a + b) IN TEN NORMAL WOMEN AND TEN WOMEN WITH PERIPHERAL RHEUMATOID ARTHRITIS

Standard of Comparison	Women				Difference between Means	Standard Error of Difference
	Ten Arthritic		Ten Normal			
	Mean	Standard Deviation ±	Mean	Standard Deviation ±		
Body-weight (kg.)	50·7	6·1	62·0	10·9	**−11·3***	4·0
Surface Area (sq. m.)	1·50	0·091	1·67	0·176	**− 0·17***	0·063
Plasma vol. (ml.)	2,650	396	2,420	278	+240	156
Plasma vol./Body-weight (ml./kg.)	52·4	5·34	39·6	5·02	**+12·8***	2·32
Plasma vol./Surface area (ml./sq. m.)	1,770	204	1,450	110	**+320***	73·4
Red Cell vol. (ml.)	1,300	195	1,540	182	**−240***	84·2
Red Cell vol./Body-weight (ml./kg.)	25·8	3·27	25·3	2·09	+ 0·5	1·44
Red Cell vol./Surface area (ml./sq. m.)	868	110	927	70·9	−59	132
Total Blood vol. (P.V.+R.C.V.) (ml.)	3,950	496	3,960	422	−10	206
Total Blood vol./Body-weight (ml./kg.)	78·2	6·15	64·9	7·50	**+13·3***	3·1
Total Blood vol./Surface area (ml./sq. m.)	2,640	232	2,380	134	**+260***	86·2
Body Haematocrit $\left(\frac{6}{3+6} \times 100\right)$ (per cent.)	33·0	3·87	39·0	2·40	**− 6·0***	1·44
Corrected Venous Haematocrit (per cent.)	36·3	4·34	42·0	1·57	− 5·7	1·46
Body/Venous Haematocrit Ratio	0·912	0·048	0·932	0·037	− 0·0198	0·055

* Differences in bold type are significant.

that the differences observed had arisen by chance. The method has been applied to the covariances of

(1) weight and red cell mass,
(2) weight and plasma volume,
(3) weight and total blood volume.

The third relationship is illustrated in Fig. 3; this is a scattergram of the values for weight and total blood volume, in which the slopes of the mean regression lines for patients and controls are not significantly different, hence a comparison of the two sub-groups about the regression line for all the subjects is valid. This line has been drawn in and represents the equation:

Blood volume (ml.) = 3956·65 + 39·84 × (body-weight (kg.)—55·38).

Fig. 3(*a*) shows how the means of the two sub-groups differ both in weight and in blood volume. They have consequently been adjusted to the point

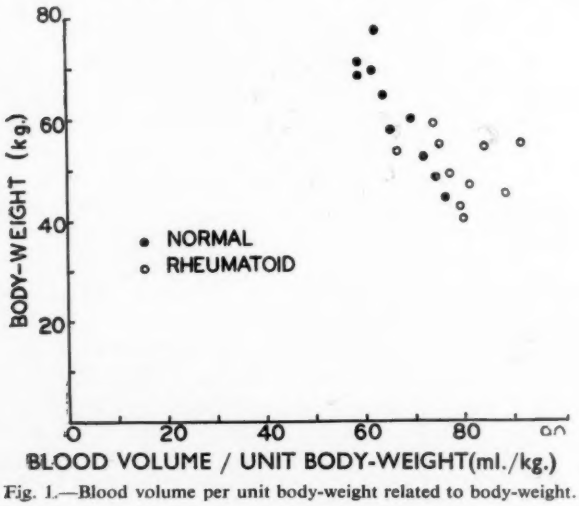

Fig. 1.—Blood volume per unit body-weight related to body-weight.

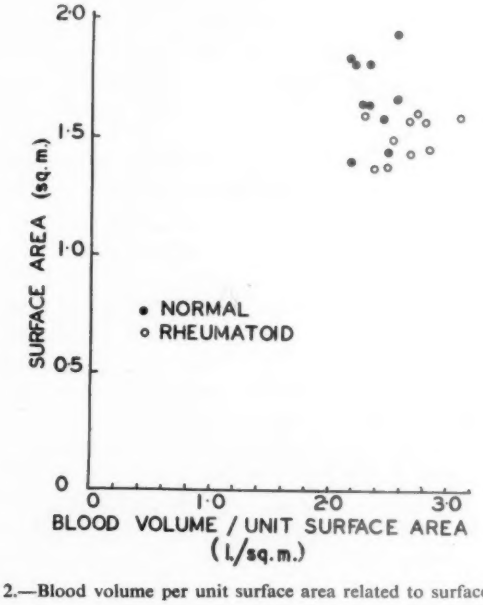

Fig. 2.—Blood volume per unit surface area related to surface area.

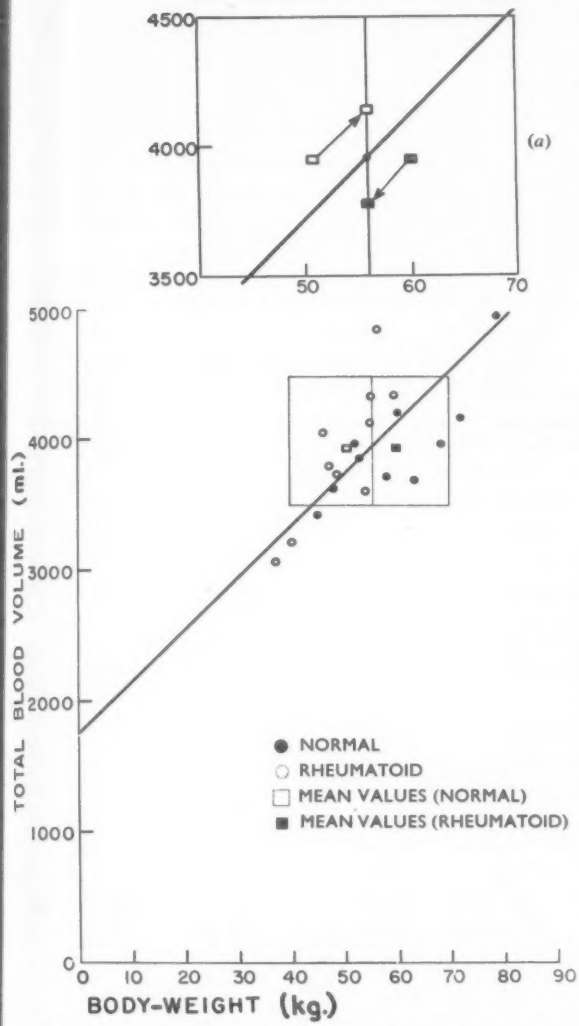

Fig. 3.—Body-weight related to blood volume. The slope is the regression line for all observations. Enlarged inset (*a*) shows how the means of controls and rheumatoid subjects differ in body-weight and blood volume.

corresponding to the average weight of the subjects as a whole by moving them parallel to the mean regression line. When this is done and the two groups are compared for the values they would have had if they had been of equal weight, it is found that the arthritis subjects have a greater total blood volume than the controls, and the difference, as judged by the "*t*" test, is significant.

Table VI summarizes the results for the three relationships.

TABLE VI

ADJUSTED MEAN VALUES FOR RED CELL MASS, PLASMA VOLUME, AND BLOOD VOLUME IN TEN NORMAL WOMEN AND TEN WOMEN WITH PERIPHERAL RHEUMATOID ARTHRITIS
(Adjusted mean values for volumes)

Measure of Volume	Arthritics	Normals	Difference ± S.D.	Change (difference/normal × 100) per cent.
Red Cell Mass (ml.)	1,370	1,470	100±72	− 7·1
Plasma (ml.) ..	2,770	2,300	470±44*	+20·4
Total (ml.)	4,140	3,780	360±52*	+ 9·6

* The difference is significant.

We conclude that the chief cause of the anaemia in our patients was 20·4 per cent. rise in the plasma volume, which was statistically significant. An average fall of 7·1 per cent. in the red cell mass failed to reach significance levels. The total blood volume of the arthritis patients showed an average significant rise of 9·6 per cent. Thus our patients showed a hypervolaemic normocythaemia.

Serial Simultaneous Blood Volume Measurements in one Arthritic Patient.—A man of 32 years with rheumatoid spondylitis of 8 years' duration exhibited chiefly involvement of the spine and hips. He had been maintained in reasonably good remission for 3 years on 75 mg. cortisone acetate orally per day. On this therapy he was not anaemic and had a normal or only slightly elevated sedimentation rate, despite residual bony deformities with some pain. During the period of this study his regime and diet were constant. The observations made on the plasma volume and red cell mass were performed before and after the abrupt discontinuation of a cortisone acetate on Day 4 (Table VII).

24 hours after withdrawal of the hormone the patient experienced a recurrence of the symptoms and signs of arthritis, accompanied by a reduction in the proportion of haemoglobin and erythrocytes in the peripheral blood, without reduction of red cell mass, other than that which could be accounted for as cells (about 90 ml.) removed with blood samples drawn for concurrent metabolic studies.

TABLE VII

VALUES FOR A PATIENT WITH RHEUMATOID SPONDYLITIS BEFORE AND AFTER WITHDRAWAL OF CORTISONE ACETATE THERAPY

Day No.	Plasma Volume (Evans' Blue) (ml.)	Red Cell Mass (^{51}Cr) (ml.)	Total Volume (ml.)	Body Haematocrit (per cent.)	Corrected Venous Haematocrit (per cent.)	Body/Venous Haematocrit Ratio
1	1,940	1,390	3,330	41·8	45·2	0·925
11	2,230	1,300	3,530	36·9	38·6	0·955
Change	+290	−90	+200	−4·9	−6·6	—

Discussion

The dye retention results confirm our past experience, namely, that intravenously-injected congo red is removed abnormally rapidly from the blood stream of rheumatoid arthritis patients. The significance of this is not obvious. At least six mechanisms may influence the removal of dyes from the blood stream:

(1) biliary excretion (Smith, 1925),
(2) urinary excretion,
(3) reticulo-endothelial system (Cruickshank and Whitfield, 1944),
(4) dispersion of dye outside the vascular system because of increased capillary permeability,
(5) tissue fixation of dyes (possibly by a sub-clinical level of amyloidosis or other alteration of connective tissue),
(6) increased loss through a change in the dye-protein binding of constituents of the blood stream.

We have no evidence favouring either (1) or (3). Urinary excretion of congo red dye in the first hour was not detected in these studies or by others (Unger and others, 1948). Smith (1925) found that vital red dye stained the cervical lymph in dogs soon after intravenous injection. Both lymph flow (Drinker and Field, 1933) and capillary permeability (Krogh, 1930) are increased in inflammation, whatever its cause, and in rheumatoid arthritis the inflamed synovial membrane tends to permit the passage into the synovial fluid of increased amounts of macromolecules such as plasma proteins, and even at times bacteria (Bauer and others, 1940). Nevertheless, the rate of movement of dye to the synovial fluid in the two cases studied suggests that it is unlikely that significant amounts of dye leave the blood stream by this route during the first hour after injection.

One possible exception is Case 22 (Table IV), in whom the Evans' blue dye method for measuring blood volume gave unexpectedly high results. This patient's arthritis was associated with marked and lifelong peripheral oedema of the type seen in Milroy's disease. Moreover, the rate of removal of Evans' blue dye from the blood stream in the patients was only slightly (although significantly) faster than in the controls. It is possible that the comparatively low rate of retention of congo red in the blood stream in arthritis subjects represents a subclinical level of amyloidosis or analogous alteration of the polysaccharide and protein constituents of connective tissue. Two points favour this interpretation. Firstly, amyloid has been found in the tissues of 24 per cent. of eighty patients with rheumatoid arthritis submitted to autopsy in this hospital (Bauer and Bennett, unpublished). In one of these congo red retention was in the 50-70 per cent. range shortly before death (Mass. Gen. Hosp., 1948). Secondly, decreased congo red retention has been found in other patients who, although without clinical evidence of amyloidosis, did have diseases which can be associated with this complication. However, in two patients in whom the congo red retention was found to be 50 per cent, or less within 2 weeks of death, there was no gross or histological evidence of amyloidosis at autopsy despite using several staining techniques; one of these has been published (Mass. Gen. Hosp., 1941). Finally, we found no evidence for the possibility that alteration in the plasma proteins might account for changes in dye-retention, or that a constituent of the blood of rheumatoid arthritis patients might directly alter the intensity of the colour of congo red dye. We leave unexplained the tendency of the congo red method to measure an anomalously large plasma volume in arthritis. It seems likely that part of the dye is rapidly removed from the circulation in some patients during the first few minutes following injection, and that the remainder is lost at a slower rate, though more rapidly than the rate of loss of Evans' blue dye. The one patient with amyloidosis gave high blood volume values for both of these dye methods. In the absence of such complications, however, the Evans' blue method is reliable for measuring blood volume of both rheumatoid arthritis and normal subjects.

No attempt will be made to review the literature on blood volume measurement except to note that estimates of the normal blood volume vary with the method employed. Methods depending on the dilution of labelled red blood cells give figures 10 to 20 per cent. lower than methods depending upon the dilution of a substance distributed in the plasma. Other sources of variation between laboratories include differences in such details as the type of haematocrit tube used, the time and force with which the blood is centrifuged, the correction for trapped plasma, and the time that the tourniquet is left on the arm preparatory to venepuncture. Comparisons also vary with the standard of reference: the use of body-weight, for example, may introduce errors, because blood volume tends to be proportionately higher in lighter subjects (Gibson and Evans, 1937; Rowntree and others, 1929). For these reasons we compared the values for blood volume and its component parts in rheumatoid arthritis subjects with those of a matched series of normal subjects in the same laboratory making a statistical correction for body-weight differences: on the other hand we may have introduced errors of sampling because of the relatively small numbers (10 + 10) of patients and

controls studied. We are aware that the method of comparison of normal and arthritis subjects is a major problem in numerical studies of this sort, and that the apparent result may be influenced markedly by the method or standards of reference chosen. It is of interest that of the three methods of comparison studied (volume per unit body-weight, volume per unit surface area, and covariance of blood volume and body-weight), the method chosen is that which gives the smallest differences of blood volume and plasma volume between the two groups.

Few authors who have studied the normal blood volume by methods similar to those used here give their results in sufficient detail to enable one to distinguish subjects who are comparable to our normals for age and sex. Friedlander and co-workers (1935), using Evans' blue dye, found a mean blood volume of 80·2 ml./kg. for twenty women of mean age 41, results which are probably too high, since they are well above the normal ranges reported by others. Gibson and Evans (1937), using the same method in a younger series of women whose average age was 31·5 years, found 61·1 ml./kg. or 2·53 l./sq. m. Their older subjects had lower blood volumes (see Table VIII). For red cell tagging methods, Berlin and others (1951), using phosphorus ^{32}P, reported 64·6 ml./kg. in a group of fifteen normal women of average age 31·3 years and average weight 55·7 kg. No results for normal women have been published for the ^{51}Cr method.

Four reports are available on the blood volume in rheumatoid arthritis. Sparks and Haden (1932) used the congo red method and reported an increase compared with normal subjects. Robinson (1943) used phenol-tetra-brom-phthalein-sodium sulphate dye and came to the same conclusion. Garry (1952) used Evans' blue and found an increase in plasma volume and a decrease in red cell mass. His conclusions are weakened because the weights of his patients are all multiples of 5 or 10 kg. The most comprehensive study of this subject is that of Jeffrey (1953), who used Evans' blue in a series of 52 patients with rheumatoid arthritis, and concluded that total blood volume was normal or reduced in this disease. He found a raised blood volume per unit weight in his thirty women patients, but attributed this to the loss of weight they had experienced rather than to an increase in blood volume. Their blood volume per unit surface area was not significantly increased. Jeffrey compared his results with the normal figures of other workers, chiefly Gibson and Evans (1937), which may have introduced an error due to differences in technique. Moreover, in normal women blood volume decreases as age increases (Gibson and Evans, 1937; Rowntree and others, 1929). Jeffrey does not state the age of his patients, but rheumatoid arthritis is commonest in women over 30 years of age, so that one would suspect that his arthritis patients were older than the normal subjects of Gibson and Evans, most of whom were younger than this.* Jeffrey's figures for blood volume/unit surface area are significantly greater than those for the ten oldest normal women in Gibson and Evans's series for whom surface area data are available (Table VIII).

Finch and others (1951) used the Evans' blue method in a group of twenty patients, seventeen of whom had rheumatoid arthritis, and reported a mean decrease in the blood volume, compared with the normal figures of Gibson and Evans (1937), with height as the standard of reference. They do not give enough data for us to analyse whether factors such as age, sex and body-weight could have influenced this comparison.

Chaplin and others (1953) and Verel (1954) stressed the constancy of the ratio of the "whole body" haematocrit to the peripheral haematocrit in the absence of splenic enlargement. In our patients

* A misprint in Gibson and Evans' paper gives 38·9 as the average age of his women subjects. This should apparently have been 31·5 years.

TABLE VIII

COMPARISON OF JEFFREY'S RESULTS WITH THOSE OF GIBSON AND EVANS

Authors	Date	Series	Age	Surface Area (sq. m.)	Plasma Volume (l./sq. m.)	Blood Volume (l./sq. m.)
Gibson and Evans	1937	Ten oldest normal subjects for whom surface area available (*a*)	43·5 ± 5·8	1·52±0·14	1·315±0·123	2·270±0·223
Jeffrey	1953	Thirty patients with Rheumatoid Arthritis	Not stated	Not stated	1·770±0·270	2·670±0·410
Difference (*b*) ± Standard Error			—	—	**0·455*** ±0·063	**0·400*** ±0·101
Increase (*b*)/(*a*) × 100			—	—	**±34·6%***	**+17·6%***

* Differences in bold type are significant.

this ratio (Table V) was $0{\cdot}912 \pm 0{\cdot}048$, and not significantly different from that found for the control subjects ($0{\cdot}932 \pm 0{\cdot}037$). These figures are not significantly different from those of others* (Chaplin and others, 1953; Verel, 1954; Barnes and others, 1948; Berson and Yalow, 1952; Brady and others, 1953; Gibson and others, 1946; Gray and Frank, 1953; Meneely and others, 1947; Nachman and others, 1950; Reeve and Veall, 1949), who measured red cell mass and plasma volume simultaneously by various techniques.

Our results bear upon the problem of the anaemia of rheumatoid arthritis. Anaemia is a common feature of this disease, being present in 33 per cent. of women with rheumatoid arthritis compared with less than 10 per cent. of a matched series of normal women, and in 49 per cent. of men with rheumatoid arthritis compared with 7·4 per cent. of normal men (Lewis-Faning, 1950). The degree of anaemia that is present roughly parallels the activity of the disease process, both in groups of patients (Jeffrey, 1953) and in our experience of the long-term course of the individual patient (Giansiracusa and others, 1951). Evidence of four different kinds points away from an abnormality of the red cells and therefore toward the plasma as being the cause of this apparent anaemia.

When the other manifestations of rheumatoid disease are suppressed by cortisone acetate or adrenocorticotrophic hormone, the anaemia improves, as first noted by Hench (1952). Since this is in contrast to the effect of ACTH in normal subjects (Mason and others, 1948), we regard changes in the anaemia of arthritis provoked by changes in cortisone therapy as comparable with those occurring in spontaneous remissions and relapses. In our patients cortisone withdrawal was followed by immediate expansion of plasma volume and by anaemia without reduction in red cell mass. Conversely, patients who were treated with cortisone by Copeman and others (1952), showed an improvement in their anaemia; this was almost entirely accounted for by decrease of plasma volume in the one case in which the detailed observations are given. On the other hand, Finch and others (1951), using the Evans' blue-haematocrit method, found an absolute increase in blood volume and red cell mass in those of their patients whose anaemia improved under cortisone therapy.

Secondly, the anaemia of rheumatoid arthritis is refractory to specific haematinic therapy. Sinclair and Duthie (1950) reported success with intravenous iron, but in their study general remission of the disease could not be excluded as the cause of the improvement noted in haemoglobin concentrations and their results have not been confirmed by another team (Kuhns and others, 1950).

Thirdly, although comparatively little work has been done on some aspects of this subject, it can be said that so far no abnormality of red cell or of haemoglobin production or destruction (with one exception), or of iron absorption or metabolism has been found to cause or correlate with the anaemia of rheumatoid arthritis. The exception to this statement is red cell survival time which Friereich (1954), using the technique of Ashby (1919), found to be decreased in six out of twelve patients with rheumatoid arthritis.

Fourthly, our blood volume comparisons accord with the concept of an increased plasma volume in rheumatoid arthritis.

Nevertheless, it cannot be too strongly emphasized that caution is needed in applying results derived from a selected group of ten women with arthritis to all with this disease, and that the conclusion that the blood volume in rheumatoid arthritis is expanded depends on what normals are used for comparison and on the standards of reference on which this comparison is based. The possibility of significant changes in red cell mass in rheumatoid arthritis, though not found, has not been excluded.

Summary

In 23 patients with chronic, active, rheumatoid arthritis or spondylitis, the plasma retention of congo red at the end of one hour was $55 \pm 10{\cdot}2$ per cent. of the amount injected, as compared with a one-hour plasma retention of Evans' blue of $86{\cdot}1 \pm 1{\cdot}2$ per cent. There was no correlation for individual patients between the two dye retentions.

Plasma volume measurements in the same patients showed that the congo red method frequently gave high and unreliable results in this disease. Entry of the dyes into inflamed joints did not explain these observations.

Evans' blue disappears from the circulation slightly faster in rheumatoid arthritis than in normal subjects. The difference, though significant, does not affect the reliability of this dye in measuring blood volume in this disease. Plasma volume measurements in one patient with amyloidosis were unreliable with both dyes.

Cortisone acetate treatment was abruptly stopped in one patient with rheumatoid spondylitis who had been maintained in clinical remission with the aid of this hormone. Both arthritis and anaemia promptly recurred, and serial measurements sug-

* Haematocrits corrected where necessary, × 0·97 for trapped plasma.

gested that the anaemia was the result of expansion of the plasma volume.

Plasma volume by the Evans' blue method and red cell mass by the radio-active sodium chromate method were measured simultaneously in ten women with typical moderately severe active peripheral rheumatoid arthritis and in ten normal women, matched as closely as possible for age. The arthritis patients were more anaemic than the normals; this difference was associated with a significant increase of plasma volume of 20·4 per cent., and a significant increase of blood volume of 9·6 per cent. A 7·1 per cent. fall in red cell mass failed to reach significance levels. It is not likely that expansion of the plasma volume is the only cause for the anaemia of rheumatoid arthritis in all patients with this disease.

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Arthrite rhumatismale: l'étude de la rétention des colorants et la comparaison des colorants et des globules rouges radioactivement marquées dans les procédés de mesure du volume sanguin

RÉSUMÉ

Chez 23 malades atteints d'arthrite rhumatismale chronique et active ou de spondylite, la rétention par le plasma du rouge Congo au bout d'une heure fut $55 \pm 10{,}2$ pour cent de la quantité injectée et celle du bleu d'Evans $86{,}1 \pm 1{,}2$ pour cent. Il n'y eut pas de corrélation pour des malades individuels entre les pourcentages de rétention pour chaque colorant.

La mesure répétée du volume du plasma chez de mêmes malades montra que le rouge Congo donne souvent des chiffres élevés et peu fidèles dans cette maladie. La pénétration des colorants dans les articulations enflammées n'explique pas ces observations.

Le bleu d'Evans dispara t de la circulation un peu plus vite chez les rhumatisants que chez les hommes normaux. Cette différence, bien que significative, ne concerne pas l'exactitude de ce colorant comme indicateur du volume sanguin dans cette maladie. Le mesure du volume plasmatique chez un malade atteint de dégénérescence amyloïde donna des résultats imprécis avec les deux colorants.

On arrêta brusquement l'administration d'acétate de cortisone à un malade atteint de spondylite rhumatismale, jusqu'à alors en état de rémission grâce à cet hormone. L'arthrite et l'anémie retournèrent rapidement, et une série de déterminations indiqua que l'anémie résulta de l'expansion du volume plasmatique.

On détermina simultanément le volume plasmatique à l'aide du bleu d'Evans et la masse des globules rouges à l'aide du chromate de soude radioactif chez 10 femmes atteintes d'arthrite rhumatismale périphérique active et de gravité modérée et chez 10 femmes normales d'âges

correspondants. Les arthritiques furent plus anémiques que les normales; cette différence fut associée à une augmentation appréciable du volume plasmatique de 20,4 pour cent et à une augmentation appréciable du volume sanguin de 9,6 pour cent. Une diminution de la masse des globules rouges de 7,1 pour cent manqua la limite de la signification statistique. Il est peu probable que l'expansion du volume plasmatique soit la seule cause de l'anémie rhumatismale chez tous les rhumatisants.

Artritis reumatoide: estudio de la retención de los colorantes y comparación de los colorantes con los eritrocitos marcados radioactivemente en los procedimientos de medida del volumen sanguíneo

SUMARIO

En 23 enfermos con artritis reumatoide crónica activa o con espondilitis, la retención en el plasma del rojo Congo al cabo de una hora fué el 55 $\pm$10,2 por ciento de la cantidad inyectada y la de azúl de Evans el 86,1 $\pm$1,2 por ciento. No hubo correlación para enfermos individuales entre los porcentages de retención de cada colorante.

Midiendo repetidamente el volumen plasmático en los mismos enfermos se pudo ver que el rojo Congo produce a menudo cifras altas e inciertas. La penetración de los colorantes en las articulaciones inflamadas no explica estas observaciones.

El azúl de Evans desaparece de la circulación algo más pronto en los reumáticos que en los sujetos normales. Esta diferencia, aunque significativa, no atañe la precisión de este colorante como índice de volumen sanguíneo en esta enfermedad. La medida del volumen plasmático en un enfermo con amiloidosis dió resultados de poca precisión con ambos colorantes.

Se interrumpió de repente la administración de acetato de cortisona a un enfermo con espondilitis reumatoide, sostenido hasta entonces en remisión con esta hormona. La artritis y la anemia volvieron en seguida y una serie de medidas indicó que la expansión del volumen plasmático fué la causa de la anemia.

Se determinó simultáneamente el volumen plasmático con azúl de Evans y la masa eritrocitaria con cromato de sodio radioactivo en 10 mujeres con artritis reumatoide periférica activa de gravedad moderada y en 10 mujeres normales de edades correspondientes. Las artríticas fueron más anémicas que las mujeres normales; esta diferencia fué asociada a una aumentación apreciable del volumen sanguíneo de un 9,6 por ciento. La disminución de la masa eritrocitaria de un 7,1 por ciento no alcanzó el límite estadisticamente significativo. Es poco probable que la expansión del volumen plasmático sea la única causa de la anemia reumática en todos los enfermos.

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NATURE OF ANAEMIA IN RHEUMATOID ARTHRITIS

I. METABOLISM OF IRON

BY

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Anaemia of moderate severity is commonly present in patients suffering from rheumatoid arthritis. The degree of anaemia bears a close relationship to the activity of the disease. No completely satisfactory explanation of its presence has ever been advanced. In the past it has been ascribed to "toxic" depression of marrow function, iron deficiency, or a combination of these factors. Iron by mouth was usually prescribed, but results were seldom satisfactory. The characteristics of the anaemia have been studied in detail by a number of investigators in recent years, but a review of their reports reveals no general agreement as to underlying causes.

Nilsson (1948) stated that the anaemia was of a hypochromic and normocytic type. He considered that the red cells were of abnormal shape in that the mean corpuscular volume (MCV) was within normal limits, but the mean corpuscular diameter was decreased. Inadequate haemoglobinization was apparent from a reduction in the mean corpuscular haemoglobin concentration (MCHC). Jeffrey (1952, 1953a) found that the MCV was within the normal range in 74 of 100 cases examined (74 per cent.), whereas the MCHC was less than 30 per cent. (normal range 32-36 per cent.) in 97 of 136 cases (71 per cent.). Ross (1950) confirmed that the anaemia was of hypochromic, normocytic type.

Nilsson (1948) and Jeffrey (1952) examined myelograms from twelve and sixteen patients respectively. No consistent abnormality was reported, but in many instances the haemoglobinization of normoblasts was impaired and the production of immature normoblasts increased.

Cartwright and Wintrobe (1952) reported that free erythrocyte protoporphyrin was increased in ten or fifteen cases of anaemia in rheumatoid arthritis. That this increase was probably independent of changes in free erythrocyte coproporphyrin content was later shown by Krammer and others (1954). These findings were interpreted as being indications of retarded erythropoiesis. In the patients studied by Jeffrey (1953b) the free erythrocyte protoporphyrin varied widely from case to case.

A moderate increase in reticulocytes was noted by Nilsson (1948) in a number of female patients, but he found no evidence of increased haemolysis. Jeffrey (1952, 1953a) measured serum bilirubin, faecal urobilinogen, the number of reticulocytes, and the fragility of red cells in saline. He concluded that haemolysis was not a significant factor in the causation of this anaemia.

Robinson (1943) reported that the anaemia was largely produced by an increase in plasma volume. Jeffrey (1953a) did not consider that changes in plasma volume were of significance. Recently, however, Dixon (1954) has confirmed that a moderate increase in plasma volume occurs in rheumatoid arthritis. Nevertheless, it seems unlikely that mere dilution of the red cell mass could account for hypochromia or the severe degrees of anaemia sometimes encountered.

Nilsson (1948) found that in patients in an active phase of rheumatoid disease, marked hypochromic anaemia was relatively common. The relationship between the severity of the anaemia and activity of the arthritis was confirmed by Jeffrey (1952, 1953a), but the degree of hypochromia (as estimated by the MCHC) was commensurate with activity of disease only in female patients.

Abnormalities of the metabolism of iron in rheumatoid arthritis were recognized before the morphological characteristics of the anaemia had been fully described. Bruzzone and Massimello (1940) and Heilmeyer and others (1941) observed that the serum iron level was below normal. This observation has been repeatedly confirmed, and Nilsson (1948) found that hypoferraemia was most marked in patients with severe degrees of anaemia and active arthritis. Jeffrey (1953a) correlated low levels of plasma iron and hypochromia. He reported that the total iron-binding capacity of the plasma was not significantly abnormal—a finding in contrast to the increase in binding capacity found in anaemia directly due to deficiency of iron.

Despite the hypochromic character of the anaemia in rheumatoid arthritis, the response to the administration of iron has been reported as variable. Collins (1935) noted improvement in only five of twelve patients given adequate doses of oral iron. Nilsson (1948) considered that improvement of the anaemia was more directly

related to the onset of natural remission than to the administration of iron by mouth. The introduction of a preparation of saccharated oxide of iron suitable for intravenous administration was followed by reports of its use in rheumatoid arthritis. Sinclair and Duthie (1949) observed a good response to intravenous iron in sixteen of 23 anaemic patients who had shown no benefit from oral iron. Of the sixteen patients responding adequately, thirteen maintained a satisfactory haemoglobin level for periods ranging from 7 to 23 months. Good haematological response was reported in a further 22 of 28 patients, all of whom had failed to respond to oral iron (Sinclair and Duthie, 1950). Ross (1950) and Jeffrey (1952, 1953a, 1953b) confirmed the value of intravenous iron in cases where the anaemia had failed to improve on adequate doses of iron by mouth.

The failure of the majority of cases to respond to oral iron might be explained on the assumption that absorption from the gut is inadequate in rheumatoid arthritis. Nilsson (1948), using 0·5 g. iron lactate as a test dose, considered that absorption was impaired to some extent, especially in patients with active disease and increased erythrocyte sedimentation rate (E.S.R.). Jeffrey (1953a) reported good absorption from the gut following after a dose of 0·6 g. ferrous sulphate in six patients; three showed exceptionally low resting values of plasma iron (30-36 μg. per cent.) and a very large rise in plasma iron following the test dose. In the other three a moderate increase in plasma iron was noted. In eight cases the rise in plasma iron after the same test dose was slight and taken as presumptive evidence of impaired absorption. Sinclair and Duthie (1950) found absorption to be normal in seven anaemic patients. None responded to oral iron, but six responded satisfactorily to intravenous iron. The test dose in these cases was 1·2 g. ferrous sulphate.

From these studies it seems improbable that the superiority of intravenous iron in the treatment of the anaemia of rheumatoid arthritis can be ascribed to impairment of absorption from the gut. In a small percentage of cases frank iron-deficiency anaemia is present and response to oral or intravenous iron is satisfactory. Sinclair and Duthie (1949) observed that in the presence of a persistently high E.S.R. a satisfactory response to intravenous iron was much less frequent. Jeffrey (1953b) considered that a good response was predictable when one or more of the following features were present: low E.S.R., microcytosis, gross hypochromia, and raised total iron-binding capacity. It should be noted that these conditions occur in simple iron-deficiency anaemia and are not characteristic of the anaemia of rheumatoid arthritis.

Little information is available regarding the immediate fate of saccharated oxide of iron after its intravenous injection in human subjects, although Cappell (1930) described in detail its distribution in animal tissues. He observed that after injection the iron was rapidly removed from circulation and could be demonstrated in leucocytes and in the cells of the reticulo-endothelial system. "These cells appeared to act upon the iron"; in about 72 hours "a soluble iron compound" could be demonstrated in the plasma and this increased in amount during the following weeks. The "soluble iron" was deposited largely in the lymphatic glands and in the parenchyma cells of the liver and kidney. In the mouse, the liver, spleen, and lymphatic glands appeared to be the most important sites of iron storage. The liver parenchyma contained the greatest amount in animals killed in the later stages of the experiment. A similar distribution of iron in human subjects given large doses intravenously has been reported by Kuhns and others (1950).

From the foregoing review of the literature it would appear that the fundamental cause of anaemia in rheumatoid arthritis remains unknown and that the role of iron in the correction of this anaemia is still unexplained. In a proportion of cases which have failed to respond to adequate doses of iron taken by mouth, improvement occurs after the administration of large doses of intravenous iron. This suggests an increase in the demand for iron which cannot be met by absorption from the gut. In these circumstances it was felt that further studies of the characteristics of the anaemia and of the metabolism of iron in rheumatoid arthritis was well worth while. The object of the present communication is to present the results of the first stage of this investigation.

Material and Methods

These studies were conducted on patients suffering from rheumatoid arthritis attending the Rheumatic Unit, Northern General Hospital, Edinburgh. The majority were in-patients. Control material was obtained from members of the staff and from blood donors at the Blood Transfusion Unit, Edinburgh Royal Infirmary.

The preparation of saccharated oxide of iron (S.O.I.) used throughout these experiments was "Iviron", a colloidal solution* containing 20 mg. elemental iron per ml.

Iron.—Samples of blood were collected in iron-free centrifuge tubes, sodium oxalate (1 mg./ml.) being used as an anticoagulant when plasma was required. The method for the measurement of plasma and serum iron was essentially that described by Ramsay (1953). This method has been found to give values about 15 per cent. higher than other methods reported in the literature. Two modifications of the method were made. In order to decrease the error introduced by slight haemolysis of the blood sample, sodium sulphite (0·5 ml./0·1M) was used as the reducing agent in place of hydroxylamine (Ramsay, 1954). The final solution was centrifuged in place of the filtration recommended in the original method. This eliminated the error introduced by extraction of iron from the filter paper.

It was found that iron in the saccharated oxide is not measured by the above method unless heating of the solution is prolonged to 90 min. Identical results have been obtained by this method and by the "total iron"

* Manufactured by British Schering Limited.

method of Ramsay (1950), when solutions of S.O.I. were used. As a small percentage of the iron in S.O.I. reacts with 2-2′-dipyridyl even after heading for 5 minutes, it has been found impossible to estimate β′-globulin bound iron in the presence of S.O.I. All values stated represent the total iron content of plasma.

The method as modified for the measurement of S.O.I. was used in determination of iron in urine. Although no iron could be detected in a 24-hour sample of urine, either from normal subjects or from patients suffering from rheumatoid arthritis, recoveries of added ferrous sulphate and of S.O.I. were quantitative.

Iron-Binding Capacity.—This was estimated by the method of Rath and Finch (1949).

Plasma Protein Fractions.—Plasma proteins were precipitated by appropriate concentrations of Na_2SO_3 (Howe, 1921) and the protein estimated by the method of Lowry and others (1951). Bovine fibrinogen was used as the standard. The method was checked periodically by nitrogen determinations using the micro-Kjeldahl technique.

Iron Absorption.—Ferrous sulphate 1·2 g. was given at 10 a.m. Blood was withdrawn for measurement of serum iron at 10 a.m., 12 noon, 2 p.m., and 4 p.m. The subjects were on normal diet.

Bilirubin.—Bilirubin was measured by the method of Haslewood and King (1937), a recrystallized sample of bilirubin being used as the standard.

Bromsulphophthalein Retention Test.—The method of Mateer and others (1943) was used. The amount of dye retained 30 and 45 minutes after administration was measured.

Results

Chemical and Physical Properties of Saccharated Oxide of Iron.—Since a proprietary preparation of saccharated oxide of iron was to be used in these studies, it was considered important to examine its chemical and physical properties in detail.

"Iviron" is a stable colloidal solution of a complex of iron and a non-reducing carbohydrate residue to which the iron is very firmly bound. Boiling with N-HCl or N-NaOH releases the iron and the solution then reduces Benedict's reagent. Iron may also be liberated, but more slowly, by incubation of S.O.I. at 37° C. with the following reagents: hydroxylamine 0·3 per cent.; sodium sulphite 0·2 M; cysteine 0·2 M; hydroquinone 0·3 per cent.; ascorbic acid 0·002 per cent.; sodium hydrosulphite 0·025 per cent.; plasma. Although both sodium hydrosulphite and hydroxylamine liberated more iron from the S.O.I. complex than did sodium sulphite, they are unsuitable for routine estimation for reasons already discussed.

S.O.I. diluted 1 : 1 with saline dialyses only slowly through Visking cellulose tubing, but when subjected to ultrafiltration using Gradacol membranes of known porosity it is possible to show that the solution is non-homogeneous. With pore diameters of 6, 23, and 58 mμ, 7, 40, and 95 per cent. respectively of the iron could be recovered in the filtrates. When S.O.I. was diluted in plasma (1 : 400) no iron could be detected in the ultrafiltrate. A possible explanation of this would be the adsorption of iron on protein. To examine this possibility, plasma containing S.O.I. was subjected to paper electrophoresis under conditions described by Kerr and Ramsay (1954). Over the *p*H range 7·1-8·6 S.O.I. was found to be preferentially adsorbed on to the filter paper and only the β′-globulin bound iron could be detected in the protein fractions by the method given by Kerr and Ramsay (1954). The quantity of this iron was probably increased by small amounts of iron liberated by slow hydrolysis of S.O.I. during the 18 hours required for separation of the proteins.

S.O.I., even in the presence of protein, is easily adsorbed from solution by cellulose, alumina, and certain ion exchange resins. As a method of determining the association, if any, of S.O.I. and protein, the plasma protein fractions were precipitated with $(NH_4)_2SO_4$, Na_2SO_3, or cold ethanol (Cohn and others, 1946). From these experiments, using plasma to which S.O.I. had been added to give an iron concentration of 4-6 mg./100 ml., it appeared that S.O.I. was firmly bound by the fibrinogen fraction and only loosely bound by the globulin and albumin fractions. The fibrinogen-S.O.I. complex was not dissociated by washing with saline or by reprecipitation, and chemical analysis showed that 1 μg. iron combined with approximately 50 μg. fibrinogen. In both plasma and serum the albumin and globulin complexes were found to be much less stable, and analysis suggested a ratio of 1 : 1,000 rather similar to that of iron in the β′-globulin fraction.

Using plasma and serum in which the concentration of S.O.I. was reduced to 1 mg. Fe/100 ml. no stable protein-S.O.I. complex was found.

Plasma Iron Levels in Normal Subjects and in Patients suffering from Rheumatoid Arthritis.—In 35 healthy males the mean level of plasma iron was 181 μg./100 ml. with a standard deviation of 25 μg. In 21 male patients suffering from rheumatoid arthritis, the mean value was 113 μg./100 ml., the standard deviation being 30 μg. The corresponding figures for 35 healthy females and 46 female patients were 135 ± 21 μg./100 ml. and 100 ± 26 μg./100 ml. respectively.

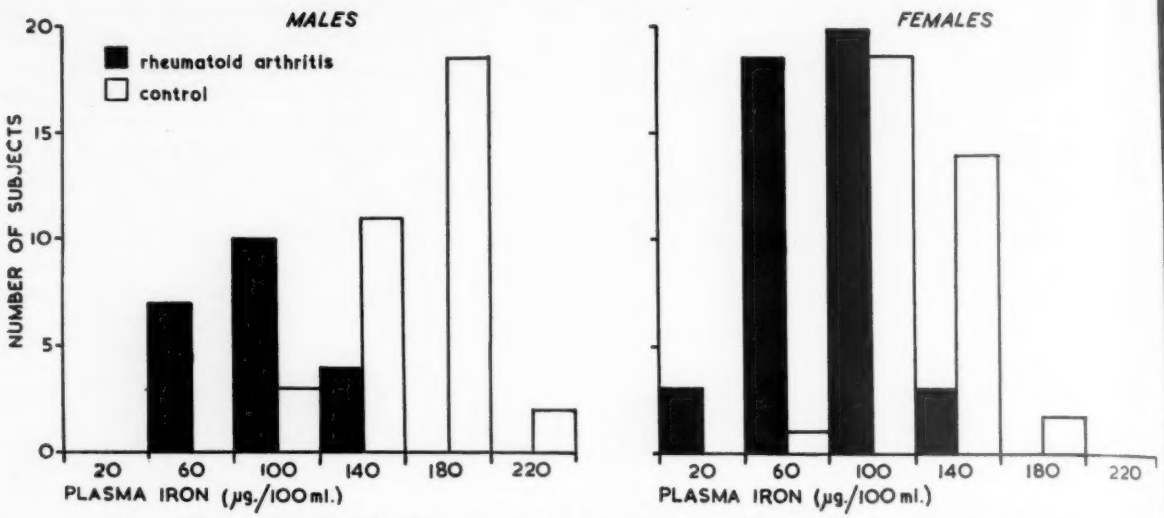

Fig. 1.—Plasma iron concentrations in seventy controls and 67 patients suffering from rheumatoid arthritis, by sex.

Fig. 1 shows the distribution of the plasma iron values in both sexes, healthy and diseased; the values in the patients are lower than those in controls. The difference of the means is 68 and the standard error 7·7919 in the case of the male groups and 35 and 7·0495 respectively in the case of the female groups. Thus both differences are highly significant.

The total iron-binding capacity of the β′-globulin fraction was determined in 42 patients. No significant difference from the values quoted by Rath and Finch (1949) for normal individuals was found (Table I).

Iron Absorption.—The results appear in Table II (opposite). Serum iron levels before administration of the test dose ranged from 45-125 μg./100 ml. in the rheumatoid group (mean 87 μg./100 ml.). In the normal subjects, none of whom was anaemic, the range was from 90-207 μg./100 ml. (mean 158 μg./100 ml.). After the administration of 1·2 g. ferrous sulphate the rise in serum iron ranged from 42-202 μg./100 ml. (mean 102 μg./100 ml.) in the rheumatoid group, and from 72-185 μg./100 ml. (mean 110 μg./100 ml.) in normal subjects. In one case of rheumatoid arthritis and in one normal subject no rise of serum iron occurred.

Distribution of Iron between Plasma and Serum after the Intravenous Injection of S.O.I.—After the injection of 10 ml. of the solution of S.O.I., the distribution of iron between serum and plasma was studied in three normal individuals and eight rheumatoid patients. Examples of the results of these experiments are shown in Fig. 2 (opposite).

The concentration of iron was greater in plasma than in serum in all instances where the iron level exceeded 1,000 μg./100 ml. It was possible to show by precipitation that this additional iron was associated with the fibrinogen. The level of fibrinogen in the plasma did not appear to bear any relationship to the quantity of iron adsorbed, both normal subjects and patients with marked elevation of fibrinogen giving similar results. It would appear that below the apparently critical level of 1,000 μg. Fe/100 ml. S.O.I. does not combine with fibrinogen.

Plasma iron concentrations were determined at daily intervals after a single injection of 10 ml. S.O.I. The mean result for seven normal subjects and

TABLE I

TOTAL IRON-BINDING CAPACITY OF PLASMA IN CASES OF RHEUMATOID ARTHRITIS AND CONTROLS

Sex	Rheumatoid Arthritis			Controls*		
	Mean Value (μg. Fe/100 ml.)	Standard Deviation	Number of Observations	Mean Value (μg. Fe/100 ml.)	Standard Deviation	Number of Observations
Male ..	322	±36	14	311	±40	15
Female ..	298	±27	28	288	±57	15

* Figures quoted from Rath and Finch (1949), the standard deviation being calculated from the data in Table II of that paper.

TABLE II

ABSORPTION OF IRON (AS FERROUS SULPHATE) IN CASES OF RHEUMATOID ARTHRITIS AND CONTROLS
(Test Dose 1·2 g. Ferrous Sulphate)

Diagnosis	Sex	Serum Iron (μg./100 ml.)				
		Before Test Dose	After 2 hrs	After 4 hrs	After 6 hrs	Maximum Rise
Rheumatoid Arthritis	M	111	126	204	180	93
		84	165	165	87	81
		90	204	144	99	114
		78	162	210	105	132
		105	144	159	108	54
		63	105	75	69	42
		90	222	228	180	138
		45	105	198	96	153
	F	75	120	90	81	45
		90	165	225	183	135
		123	189	246	159	123
		102	126	189	216	114
		68	252	270	243	202
		93	93	93	93	0
Control	M	207	222	270	315	108
		153	159	204	225	72
		177	177	—	177	0
		180	180	345	360	180
	F	169	300	240	183	132
		90	183	276	264	186
		165	213	246	—	81
		123	216	244	219	121

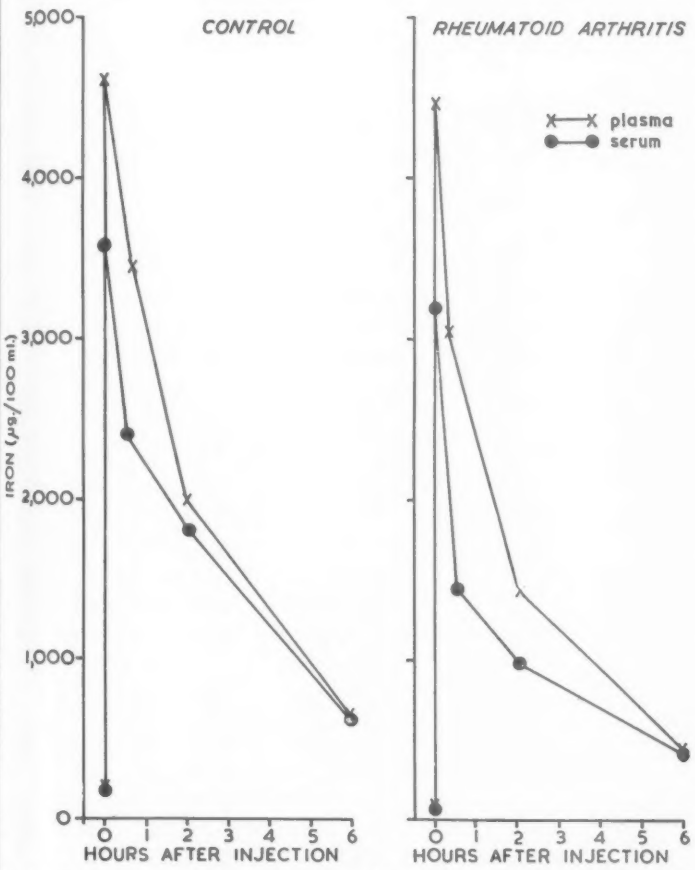

Fig. 2.—Typical curves showing distribution of iron between plasma and serum after injection of 10 ml. saccharated oxide of iron in a control and a patient suffering from rheumatoid arthritis.

seventeen patients suffering from rheumatoid arthritis are given in Fig. 3 (overleaf). In rheumatoid patients the injected iron has been cleared from the plasma within 24 hours. In normal subjects clearance was not complete until 72 hours had elapsed. In three patients in the rheumatoid group the plasma iron concentration 24 hours after injection remained above their pre-injection level.

To ascertain whether similar results would be obtained in anaemia of different origin, observations were made in one case of pernicious anaemia, one case of iron deficiency anaemia, and one case of idiopathic steatorrhoea with normoblastic anaemia (Table III, overleaf). In all three patients plasma iron measured at 24 hours was still well above the pre-injection levels, corresponding to the pattern obtained in controls.

Urinary Excretion of Iron after Injection of S.O.I.—To exclude the possibility that the more rapid clearance of S.O.I. from the plasma of patients suffering from rheumatoid arthritis might be due to an increase in the urinary excretion, urine was collected at hourly intervals after the injection of 10 ml. S.O.I. and the iron content measured.

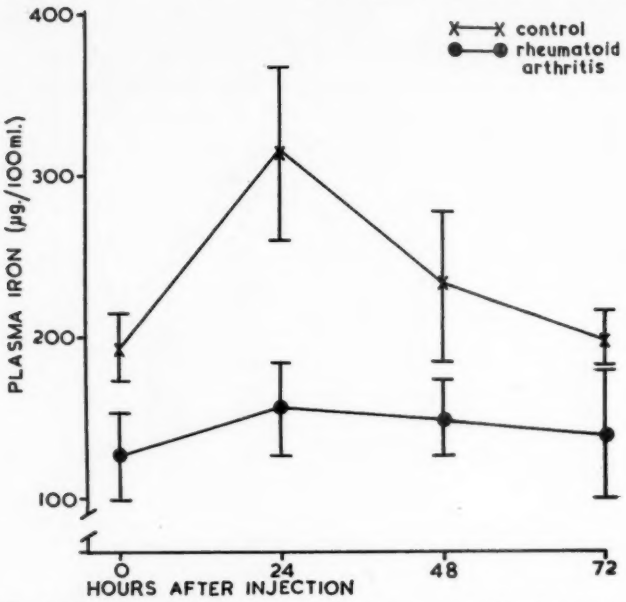

Fig. 3.—Average plasma iron concentration in seven controls and seventeen patients suffering from rheumatoid arthritis after intravenous injection of 10 ml. saccharated oxide of iron. Each ● indicates the mean of seventeen observations and the standard deviation at a given time; each × indicates the mean of seven observations and the standard deviation at a given time.

TABLE III
PLASMA IRON CONCENTRATION AFTER INJECTION OF 10 ml. S.O.I. IN PATIENTS WITH OTHER FORMS OF ANAEMIA

Diagnosis	Plasma Iron (μg./100 ml.)	
	Pre-Injection	24 hrs after Injection
Pernicious Anaemia ..	141	300
Iron-deficiency Anaemia ..	46	99
Idiopathic Steatorrhoea ..	60	450

Table IV shows that the maximum excretion of iron occurred during the first 2 hours after injection, corresponding to the highest concentrations of iron in the plasma.

TABLE IV
EXCRETION OF IRON MEASURED AT HOURLY INTERVALS AFTER INTRAVENOUS INJECTION OF 10 ml. S.O.I. IN THREE CASES OF RHEUMATOID ARTHRITIS

Time after Injection (hrs)	Total Iron (μg.)		
	Case A	Case B	Case C
1	2,420	2,372	815
2	1,083	1,056	1,851
3	532	447	588
4	304	305	307

Urine was collected for 6 hours after injection in seven normal subjects and sixteen patients. The mean value for iron excreted by the normal group was 6,114 μg. ± 1,280 μg., and that for the patients was only 3,219 μg. ± 1,301 μg.

It seemed possible that, as the saccharated oxide of iron preparation had been found to be non-

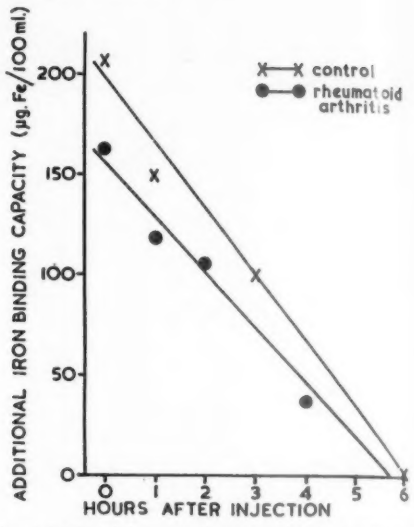

Fig. 4.—Additional iron-binding capacity in controls and in patients suffering from rheumatoid arthritis after intravenous injection of 10 ml. saccharated oxide of iron.

homogeneous, the excreted fraction might be of lower molecular size. From the method of analysis it was known that the iron excreted was still in the saccharated form, maximum colour being developed only when heating was continued for 90 minutes. When S.O.I. was added to urine in suitable concentration and the solution dialysed overnight against distilled water at 0° C., it was found that 5-10 per cent. of the iron passed through the membrane. If, however, urine excreted during the first few hours after injection of S.O.I. was treated in a similar fashion, 30-40 per cent. of the iron was in the dialysate. This would indicate a preferential excretion of the smaller particles of S.O.I.

Iron-Binding Capacity of Plasma after Injection of S.O.I.—It is obvious that S.O.I. could not saturate the metal-combining β′-globulin fraction, but that iron liberated by hydrolysis of the saccharated compound can combine with this protein. The binding capacity of plasma was determined in normal individuals and in patients suffering from rheumatoid arthritis at intervals after injection of S.O.I. From the data presented in Fig. 4, it is obvious that a slow hydrolysis of S.O.I. occurs in the body with subsequent saturation of the β′-globulin with iron. The amount of iron required to saturate the β′-globulin is very small (approx. 16 mg.) in comparison with the iron injected as S.O.I. (200 mg.).

Effect of a Single Injection of S.O.I. on Plasma Bilirubin.—An investigation of the plasma bilirubin levels was undertaken in seven normal subjects and nine patients suffering from rheumatoid arth-

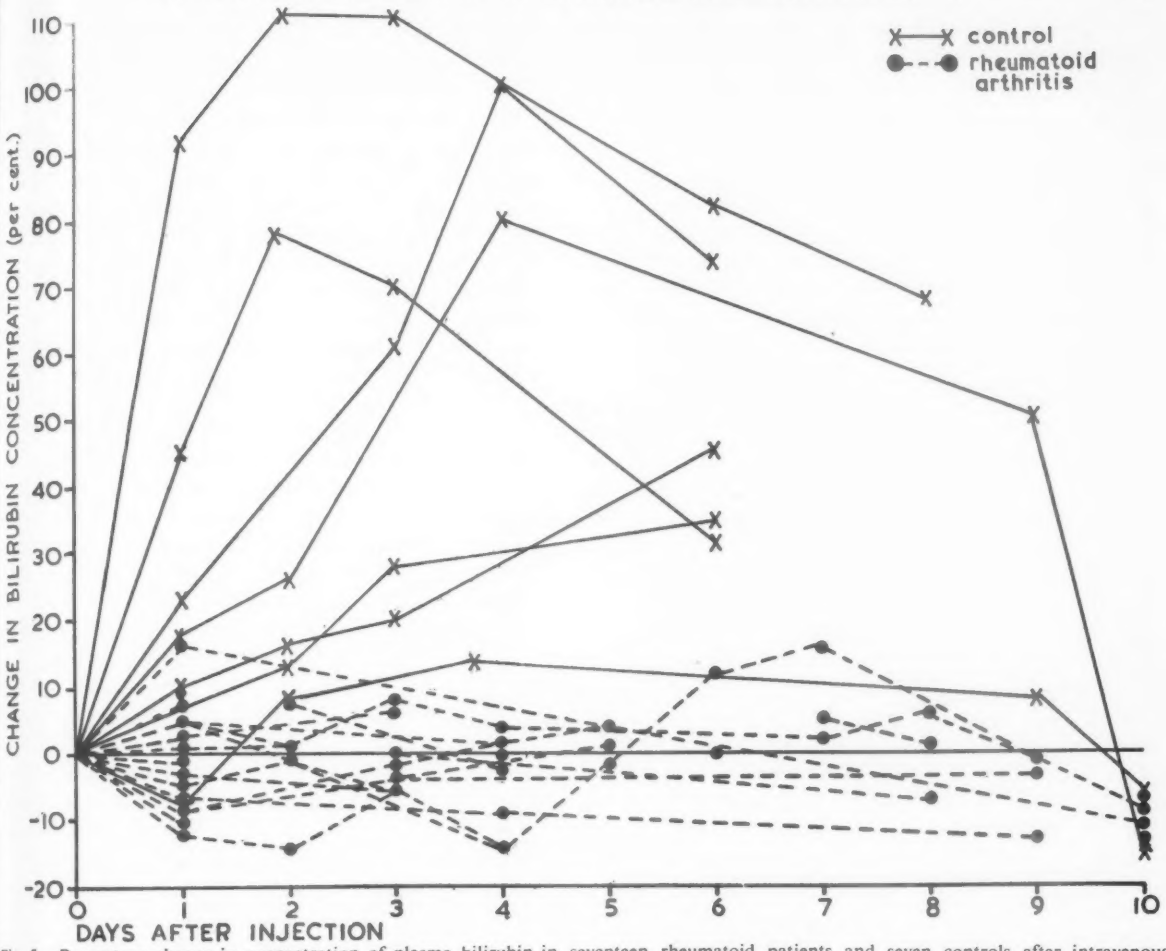

Fig. 5.—Percentage change in concentration of plasma bilirubin in seventeen rheumatoid patients and seven controls after intravenous injection of 10 ml. saccharated oxide of iron.

ritis. Only in the normal group was any change noted (Fig. 5). After a delay of 1-3 days there was a rise in the bilirubin concentration, which did not, however, exceed normal limits (1 mg./100 ml.). The concentration fell to the pre-injection level in 9 days.

As these results suggested transient impairment of liver function, the B.S.P. retention test was performed before injection of S.O.I., 3 days after injection (when the maximum change in bilirubin concentration was found), and 7 days after injection when the bilirubin concentration had returned to pre-injection value.

Table V records changes in the B.S.P. retention test which occurred in four normal subjects in whom

TABLE V

PERCENTAGE OF BROMSULPHOPHTHALEIN RETAINED AFTER INJECTION OF 10 ml. SACCHARATED OXIDE OF IRON

Diagnosis	Before Injection		3 days after Injection		7 days after Injection	
	Bilirubin (mg. %)	Per cent. Retention of Bromsulphophthalein	Bilirubin (mg. %)	Per cent. Retention of Bromsulphophthalein	Bilirubin (mg. %)	Per cent. Retention of Bromsulphophthalein
Control	0·39	0·5	0·64	1·1	0·30	0·2
	0·55	1·3	0·90	2·2	0·52	0·7
	0·53	1·2	0·88	4·1	0·49	1·0
	0·46	0·4	0·73	0·6	0·44	0·0
Rheumatoid Arthritis	0·41	2·0	0·46	1·5	—	—
	0·52	0·5	0·48	0·2	—	—
	0·36	1·3	0·40	1·4	—	—
	0·44	5·2	0·40	6·0	—	—

Retention values calculated 30 minutes after injection of bromsulphophthalein. No retention at 45 minutes was found in any case.

there was a rise in plasma bilirubin following injection of S.O.I. In four cases of rheumatoid arthritis no such rise in plasma bilirubin or change in B.S.P. retention occurred.

Discussion

Measurements of the plasma iron concentration in patients suffering from rheumatoid arthritis confirmed the presence of subnormal values, more marked in females than in males, although these levels were considerably above those found in true iron deficiency (Smith, 1952). Investigation of iron absorption from the gut revealed little evidence of impairment when the results were compared with those in normal controls given the same dose by mouth. This is in contrast to the diminished absorption reported by Cartwright and others (1946) in patients suffering from anaemia complicating infection, although these workers believe that rapid removal of iron from the plasma may partly explain the minimal rise which followed the test dose.

Before going on to study the fate of S.O.I. after injection by the intravenous route it was considered essential to define in as much detail as possible the physical and chemical properties of S.O.I. It was found that, to measure the iron content of solutions of this preparation by the method used, heating had to be prolonged to 90 minutes. Many recent reports of levels of iron in the plasma after intravenous injection of S.O.I. are of no significance because only variable fractions of the iron were measured (Cameron and others, 1951).

It has also been shown that the solution used is non-homogeneous and that the iron-carbohydrate complex is of varying molecular size. By *in vitro* experiments it was possible to show that S.O.I. in concentrations of 4 to 6 mg. Fe/100 ml. was firmly bound by fibrinogen, and combined only loosely with albumin and globulin. When the concentration of S.O.I. in plasma was reduced to 1 mg. Fe/100 ml. no linkage with protein took place. This observation was confirmed when the distribution between plasma and serum iron was studied *in vivo* after the injection of 10 ml. S.O.I. From this it is obvious that, when iron levels are measured immediately after the injection of S.O.I., plasma, not serum, must be used. The possible significance of the combination of S.O.I. with fibrinogen is not apparent at the present time.

By measurement of the iron-binding capacity at intervals after injection it was shown that it slowly fell to zero during the following 6 hours, in both normal subjects and rheumatoid patients, indicating a slow hydrolysis of the S.O.I. The combination of rapid removal and slow hydrolysis provides an explanation for the absence of toxic effects, which are believed to be due to the presence of free ionic iron (Cartwright and Wintrobe, 1949).

Daily measurement of plasma iron after a single injection of 10 ml. S.O.I. showed that in the majority of patients with rheumatoid arthritis the iron was cleared within 24 hours, whereas in normals clearance was rarely complete before 72 hours. This could not be explained by increased excretion in the urine. Rheumatoid patients were found to excrete a smaller proportion of the dose given than normal controls. Similar observations regarding the rapid clearance of non-colloidal preparations of iron from the plasma in patients with rheumatoid arthritis have been recorded by Nilsson (1948) using 10 mg. iron as iron and ammonium citrate, and by Cartwright and others (1946) using iron ascorbate (0·5 mg./lb. body-weight) in patients with anaemia complicating infections.

In view of the transfer of iron from the cells of the reticulo-endothelial system to the liver parenchyma noted by Cappell, plasma bilirubin was measured at intervals following injection. In normal subjects a small but fairly consistent rise was noted on the third or fourth day. Values returned to previous levels within 7 to 8 days. No such change was found in rheumatoid patients. Investigation of the excretory function of the liver by the bromsulphophthalein test suggested transient impairment in normal subjects, which was not evident in the rheumatoid group. Mills and Dragstedt (1936) found that there was abnormal retention of bromsulphophthalein in animals after injection of indian ink and saccharated oxide of iron. It is clear that a much more detailed study of liver function after administration of iron by the intravenous route in normal subjects and patients suffering from rheumatoid arthritis will be necessary before the significance of the differences found can be assessed, but these preliminary observations provide some additional evidence of abnormal metabolism of iron in this disease. It has been suggested by Cartwright and Wintrobe (1952) that, in the anaemia of infection, an increased demand for iron by the cells of the reticulo-endothelial system may account for the hypoferraemia and the rapid clearance of iron from the blood. They state, however, that nothing is known of the function iron may fulfil in these circumstances. The apparent derangement of iron metabolism in rheumatoid arthritis conforms to a similar pattern, although there is no evidence that infection plays a significant part in this disease. The common factor would appear to be extensive tissue damage. The relationship between anaemia

and abnormal metabolism of iron is by no means clear. The characteristics of the anaemia in rheumatoid arthritis differ significantly from those of true iron deficiency anaemia. The red cells are of normal size, the iron-binding capacity of the plasma is normal, and, although plasma iron levels are subnormal, it would appear unlikely that the reduction in both haemoglobin concentration and red cell count are explained solely by deviation of iron from the marrow. The authors have obtained unequivocal evidence (to be reported in a later communication) that the survival of normal red cells transfused to patients with active rheumatoid arthritis is substantially reduced. This would suggest that reduction in the survival time of the patient's own red cells may be of importance. In these circumstances the improvement in anaemia which follows the administration of large doses of S.O.I. intravenously may depend to some extent at least on actions other than an increase in the amount of iron available to the marrow. Cappell's observation that, in animals given saccharated oxide of iron, the metal is slowly transferred from the cells of the reticulo-endothelial system to those of the liver parenchyma may be of some significance in this connection. The haematological response to intravenous iron in patients with rheumatoid arthritis may not attain its maximum for 2-3 months; there is no correlation between plasma iron levels and improvement in the anaemia, and the amount of S.O.I. required to produce a response is often far in excess of that calculated to restore the haemoglobin concentration to normal. These preliminary studies have not revealed the cause of anaemia in rheumatoid arthritis, but the presence of marked abnormality in the metabolism of iron in this disease has been confirmed. The mode of action of iron complexes given intravenously is not clear, but it is felt that a more complete knowledge of their initial distribution and ultimate localization is of great interest.

Summary

(1) Previous work on the nature of anaemia in rheumatoid arthritis and the metabolism of iron in this disease has been reviewed.

(2) The existence of significant degrees of hypoferraemia in the presence of normal iron-binding capacity has been confirmed.

(3) No evidence of impaired absorption of iron from the gut has been obtained.

(4) The physical and chemical properties of a commercial preparation of saccharated oxide of iron have been examined.

(5) The rate of removal of iron from the plasma after intravenous injection of the saccharated oxide is more rapid in patients with rheumatoid arthritis than in healthy individuals. The more rapid clearance from the blood is not accounted for by excretion in the urine.

(6) Evidence of transient impairment of liver function in normal individuals after a single injection of saccharated oxide of iron has been obtained. No signs of interference with liver function have been found in patients with rheumatoid arthritis.

(7) The relationship between the derangement of iron metabolism and the occurrence of anaemia in rheumatoid arthritis is not clear, nor has any adequate explanation been found for the improvement in anaemia which follows the administration of saccharated oxide of iron in some cases.

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Nature de l'anémie dans l'arthrite rhumatismale

RÉSUMÉ

(1) On passe en revue les travaux antérieurs sur la nature de l'anémie dans l'arthrite rhumatismale et le métabolisme du fer dans cette maladie.

(2) On confirme l'existence d'une carence significative du fer sanguin en présence d'une capacité normale de fixation de cet élément.

(3) On n'a pas trouvé de preuves de l'altération de l'absorption intestinale de fer.

(4) On a étudié les propriétés physiques et chimiques d'une préparation commerciale d'oxyde saccharé de fer.

(5) Le taux d'élimination du fer sanguin après l'injection intraveineuse de son oxyde saccharé est plus grand chez les rhumatisants arthritiques que chez les sujets normaux. L'excrétion urinaire de fer ne rend pas compte de son élimination sanguine plus rapide.

(6) On a trouvé des signes d'altération passagère de la fonction hépatique après une seule injection d'oxyde saccharé de fer chez des sujets normaux. Chez les rhumatisants arthritiques on n'a pas observé de signes d'atteinte de la fonction hépatique.

(7) Le rapport entre le métabolisme ferrique dérangé et l'apparition de l'anémie dans l'arthrite rhumatismale n'est pas clair; on ne peut pas, non plus, expliquer d'une manière satisfaisante pourquoi, dans un certain nombre des cas, l'anémie s'améliore après l'administration d'oxyde saccharé de fer.

La naturaleza de la anemia en la artritis reumatoide

SUMARIO

(1) Se pasa en revista los trabajos anteriores sobre la naturaleza de la anemia en la artritis reumatoide y sobre el metabolismo del hierro en esta enfermedad.

(2) Se confirma la existencia de una hipoferemia de grado apreciable en presencia de una capacidad normal para fijar el hierro.

(3) No encontráronse indicios de deterioro de la absorción intestinal de hierro.

(4) Las propiedades físicas y químicas de una preparación comercial de óxido sacarado de hierro fueron estudiadas.

(5) La pérdida de hierro sanguíneo después de la inyección endovenosa de óxido sacarado es más rápida en enfermos con artritis reumatoide que en sujetos normales. La excreción urinaria de hierro no da cuenta de su eliminación sanguínea más rápida.

(6) Encontráronse indicios de deterioro temporal de la función hepática en sujetos normales después de una sola inyección de óxido sacarado de hierro; no se observaron signos de tal deterioro en enfermos con artritis reumatoide.

(7) La relación entre el disturbio del metabolismo férico y la ocurrencia de la anemia en la artritis reumatoide no parece clara; tampoco se puede hallar una explicación adecuada para la mejoría de la anemia en un número de casos después de la administración de óxido sacarado de hierro.

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ACTION OF HYPOPHYSEAL GROWTH AND THYROTROPHIC HORMONES IN THYROIDECTOMIZED RATS

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It has been shown (Selye, 1951b) that in unilaterally nephrectomized rats drinking 1 per cent. NaCl, electrophoretically homogeneous preparations of growth hormone (STH) caused nephrosclerosis, polyuria, myocarditis, and hypertension. This syndrome very closely resembles that produced by desoxycorticosterone acetate (DCA).

However, one striking difference between the effects of STH and DCA is that the former stimulates somatic growth but causes no visible lesions of periarteritis nodosa in mesenteric vessels, while the latter produces marked periarteritic changes but no excess growth. We have already shown (Salgado, 1954a; Salgado and Selye, 1954) that in thyroparathyroidectomized animals both DCA and MAD fail to produce hypertension; myocardial and renal lesions are much diminished but nevertheless periarteritis nodosa is more severe than in the intact animals similarly treated. We have postulated that the absence of the thyroid is probably a condition that favours the appearance of periarteritic lesions (Salgado, 1954b).

The present experiment was devised to see if, in the absence of the thyroid, STH-treated rats would develop lesions of periarteritis nodosa. At the same time, we compared, at the same dose level, the effect of STH and thyrotrophic hormone (TTH), as small amounts of the latter are present in our preparation of STH as an impurity.

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Materials and Methods

67 Sprague Dawley rats were subdivided into six groups (Table I). The right kidney was removed in all groups and thyroparathyroidectomy was performed in Groups II, V, and VI, at the beginning of the experiment.

STH (Armour R-285-183) was administered twice a day subcutaneously, dissolved in saline, the daily dose being 1 mg./50 mg. body-weight per day.

TTH (Armour P589-80) was given under the same conditions and at the same dose level as STH.

The animals received both Purina Fox Chow and 1 per cent. NaCl (as drinking fluid) *ad lib.*

Blood pressure measurements were made by the method of Friedman and Freed (1949). All animals were killed on the 28th day, except four in Group VI (killed on the 43rd day), and their organs were fixed in Susa for weighing and histological study. Sections were stained with haematoxylin and eosin as well as with the PAS procedure (McManus, 1948).

The data were statistically evaluated according to the method of Snedecor (1946).

TABLE I

ORGAN WEIGHTS IN RATS UNILATERALLY NEPHRECTOMIZED AND DRINKING 1 PER CENT. NaCl, TREATED WITH STH OR TTH

	Group	No. of Rats	Organ Weights (mg./100 g. body-weight)		
			Kidney	Heart	Adrenals
I	Control	11	795 ± 24	374 ± 11	14 ± 0·34
II	Thyroidectomy	11	650 ± 24	283 ± 11	15 ± 0·64
III	TTH	11	959 ± 56	422 ± 15	15 ± 0·9
IV	STH	11	1,330 ± 91	500 ± 22	33 ± 2·5
V	Thyroidectomy + TTH	11	726 ± 20	322 ± 10·7	16 ± 0·84
VI	*Thyroidectomy + STH	12	705 ± 19	387 ± 15	20 ± 1·2

* The figures include only the eight animals killed on the 28th day, simultaneously with the other groups.
All the weights are accompanied by the standard error of the mean.

Results

In the course of the experiment, it soon became evident that the blood pressure and the fluid intake (as well as the diuresis) rose significantly above normal only in intact rats treated with STH or TTH. Apparently thyroidectomy inhibits the salt appetite induced by STH or TTH in the intact rat (Figure).

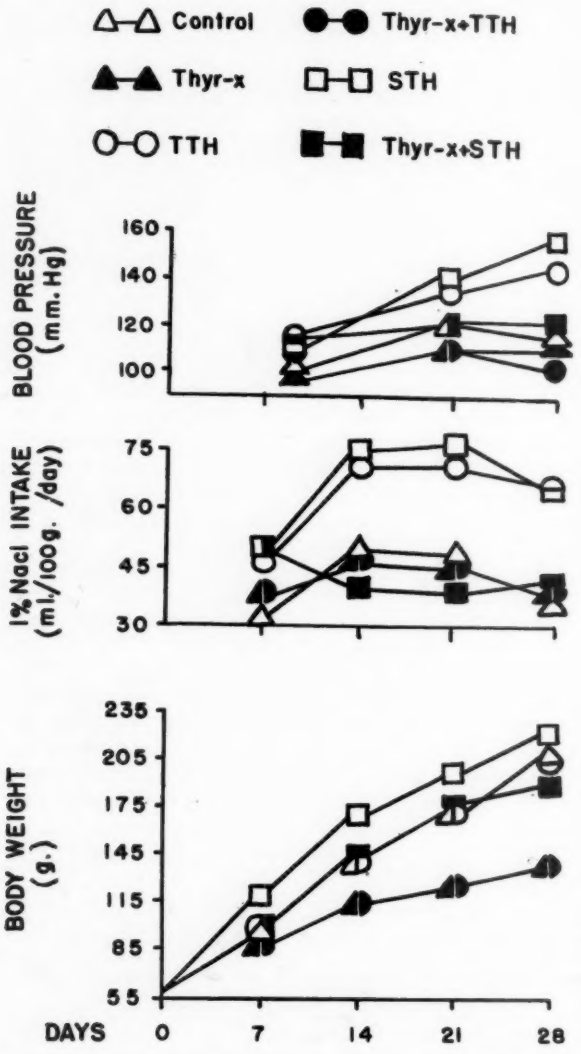

Figure.—Changes in body-weight, 1 per cent. NaCl intake, and blood pressure in unilaterally nephrectomized rats.

In thyroidectomized rats, the *somatic weight* increase was retarded in comparison with that of the intact controls; it was almost restored to normal by STH and was not affected by TTH. STH in the intact rat accelerated growth at the beginning of the experiment, whereas at the end the weight in Group IV (STH) was not different from that in the control group (Group I). This is presumably due to the fact that these animals showed (as we shall see later) signs of intoxication.

During the course of the experiment, two animals in Group VI (thyroidectomy and STH) showed evident manifestations of *arthritis* in the ankle joint; this lasted for about 10 days and gradually tended to disappear.

At autopsy, *nephrosclerosis* and *myocarditis* were present only in Groups III and IV. An attempt was made to evaluate these changes on a semi-quantitative basis, using a scale from + to +++.

Table II summarizes our findings in the intact animals treated with TTH (Group III) or with STH (Group IV).

TABLE II
INTACT RATS TREATED WITH TTH AND STH

Group	III (TTH)		IV (STH)	
	Per cent. incidence	Per cent. severity	Per cent. incidence	Per cent. severity
Nephrosclerosis	18	9	81	62
Myocarditis	27	15	100	68

Two animals in Group VI out of the eight killed early (on the 28th day), and three out of the four killed later (on the 43rd day) presented maximal lesions of *periarteritis nodosa* clearly visible to the naked eye. Macroscopically, the lesions consisted of a halo of gelatinous whitish material surrounding the mesenteric vessels and extending radially from the mesenteric ganglia to the intestinal loops.

It may be added that histological examination of the tissues confirmed the absence of lesions in Groups I, II, and V. Essentially, the same difference as at autopsy was noted between the TTH- and the STH-treated animals (Groups III and IV). The microscopic features of the changes observed after STH treatment do not deserve any detailed discussion here since they have been already described (Snedecor, 1946). We want to point out that in STH-treated animals, although no lesions of periarteritis are visible at autopsy, nevertheless upon careful histological examination they can be regularly found in the pancreatic vessels and less constantly in the vessels of the testis.

The absence of cardiac lesions was evident in all the thyroidectomized animals treated with STH (Group VI). Nephrosclerosis was absent in the eight animals of Group VI killed on the 28th day. In the four killed later, the kidneys appeared to be normal at low magnification but, upon careful examination, one could see an occasional glomerulus loaded with small hyaline granules and some scant tubular atrophy and thickening of the basal mem-

branes. These alterations were slight, however, and limited to two animals. Microscopically, lesions of periarteritis nodosa were seen to be limited in all instances to the mesenteric arteries. The lesions consisted in a slight dilatation of the arteries and the presence of an abundant pleomorphic exudate invading all the coats of the artery in which neoformation of vessels could readily be seen. In some of the arteries so affected, hyaline-like material could be seen in contact with the intima of the vessel.

The mean organ weights are listed together with their standard errors in Table I.

It will be noted that the mean *kidney* weight was greatest in the STH-treated intact rats. TTH also induced a significant ($P<0{\cdot}01$) augmentation of renal mass in comparison with the controls. The weight of the kidney in Group V (thyroidectomy and TTH) was almost ($P<0{\cdot}02$) significantly raised in comparison with Group II (thyroidectomy). STH did not increase the kidney mass in thyroidectomized animals ($P<0{\cdot}1$ between Groups VI and II). The weight of the thyroid in the controls was $16\pm0{\cdot}9$ and in the TTH-treated rats $23\pm1{\cdot}2$, the difference being statistically significant ($P<0{\cdot}01$).

Discussion

Our results are in agreement with those of Selye (1951b), in that treatment with STH of unilaterally nephrectomized rats drinking 1 per cent. NaCl results in an "overdosage syndrome" which, except for the absence of macroscopic signs of periarteritis nodosa, resembles that induced by DCA in similarly prepared animals.

The inability of Friedman and others (1954) to obtain similar results with STH may be explained by taking into consideration the facts that their animals were not unilaterally nephrectomized, and did not receive 1 per cent. NaCl as drinking fluid, and that the dose of STH was too small. We have already shown (Salgado and Selye, 1954) that unilateral nephrectomy and a generous supply of NaCl are necessary conditions to obtain an "overdosage syndrome". Furthermore, with daily doses of STH less than 1 mg./50 g. bodyweight, hypertension, polyuria, and accompanying cardiac and renal lesions appear only inconstantly (Salgado, 1954b).

We do not intend to deal *in extenso* with the question of the purity of STH preparations, nevertheless we wish to emphasize the fact that in our hands TTH was unable to fully reproduce the manifestations of STH overdosage, and this fact points indirectly to the conclusion that our preparation of STH possesses capacities which cannot be explained only on the basis of the presence of TTH. It has been shown that thyroxine given to animals receiving LAP or DCA aggravates the syndrome induced by these hormones (Selye and others, 1945). On the other hand it should be recalled that a "DCA-like" syndrome can be produced in the rat by high doses of thyroxine (Selye, 1951a). It would appear then that the output by the thyroid of thyroxine-like hormones under the influence of TTH can be made responsible, at least in part, for the hypertension and the slight kidney and heart lesions obtained in this experiment by the TTH treatment of intact rats.

Thyroidectomy influences the actions of STH in a different manner. Hypertension, renal and cardiac hypertrophy (above the intact controls), myocarditis, and increased salt appetite are absent after thyroidectomy: nephrosclerosis is virtually absent and the growth-promoting activity is slightly diminished, whereas macroscopically visible periarteritis nodosa and arthritis, never obtained in intact animals, are seen after thyroidectomy. These findings are in line with our previous observations on DCA and MAD, and strongly point to the fact emphasized in our first publication on the action of DCA in thyroidectomized rats, namely that the impairment in thyroid function seems to favour the appearance of periarteritis nodosa, whereas the other symptoms of overdosage are actually diminished. It is worthwhile at this point to mention that periarteritis nodosa is not seen in intact or thyroidectomized rats receiving thyroxine and DCA (Salgado, 1954b).

The data on the hormonal production of arthritis are rather confusing. In the experimental animals included in a recent publication (Salgado, 1954a), we investigated the incidence of arthritis. This series comprised 250 animals receiving DCA in daily doses from 100 μg. to 10 mg. during periods of up to 4 months, and 100 treated with STH. Two animals on DCA and none of the STH-treated animals were found to have arthritis. No histological studies were made, and this fact somewhat limits the extension of our conclusions as it has been shown that at microscopic examination the percentage of arthritis seems to be much higher (Pirozynski and Akert, 1949) in similarly treated animals.

It appears, then, that spontaneous macroscopically visible arthritis is a rare finding in the intact adult rat treated with STH or DCA, and this adds significance to our small number (two) of animals with evident arthritis in the present experiment.

Selye and others (1944) claimed that arthritis could be produced with DCA in the intact rat and more easily if the animals are thyroidectomized or adrenalectomized, but their series of animals was far too small, and infection should have been taken

into consideration in the evaluation of the results as many of their animals died from pneumonia. It has been shown that DCA produces arthritis in the rat only if the animals are thyroidectomized or have lesions in the adrenals (Harrison, 1951; Harrison and Barnett, 1953). Finally, Reinhardt and Li (1953) produced joint lesions with STH in adrenalectomized-castrated rats. It is possible, then, that the common trait between the results of Harrison and Barnett, Reinhardt and Li, and our own is a suppression of some antiphlogistic power of the adrenal after thyroidectomy. It is worthwhile to mention that aggravation of rheumatoid arthritis has been reported in man following thyroidectomy (Traut, 1952; Laine and others, 1954).

These experiments should be repeated in rats thyroidectomized with radioactive iodine in order to rule out a possible, though improbable, participation of the parathyroid gland.

Summary

The effect of overdosage with STH or TTH has been studied in intact and thyroparathyroidectomized rats, unilaterally nephrectomized and drinking 1 per cent. NaCl.

STH in the intact rat induces hypertension, nephrosclerosis, polyuria, myocarditis, and renal, cardiac, and adrenal enlargement. TTH under the same conditions induces slight lesions and enlargement in kidney and heart, polyuria, and hypertension. In thyroparathyroidectomized rats all these effects of TTH are abolished except for minimal renal and cardiac enlargement. STH induces periarteritis nodosa and arthritis, adrenal, cardiac, and renal enlargement, and slight lesions in the kidney. The other manifestations seen in the intact animal are absent.

These results are briefly discussed.

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Action des hormones de croissance et thyréotrope chez des rats thyroïdectomisés

RÉSUMÉ

On étudia l'effet des doses excessives d'hormones somatotrope (STH) et thyréotrope (TTH) sur des rats intacts et sur des rats privés de leur thyroïde, parathyroïde, d'un rein et buvant une solution de NaCl à 1%.

La STH chez des rats intact produit de l'hypertension, nephrosclérose, polyurie, myocardite et hypertrophie rénale, cardiaque et surrénale. La TTH dans les mêmes circonstances produit des lésions mineures et une augmentation de volume du rein et du coeur, polyurie et hypertension. Chez des rats thyréoparathyréoprives tous ces effets de la TTH sont abolis, à l'exception d'une hypertrophie minime du coeur et du rein. La STH produit la périartérite noueuse et l'arthrite, l'hypertrophie surrénale, cardiaque et rénale et de légères lésions rénales. Les autres manifestations observés chez les animaux intacts sont absentes.

On discute brèvement ces résultats.

Acción de las hormonas de crecimiento y tireotrópica en ratas tiroidectomizadas

SUMARIO

Se estudió el efecto de dosis excesivas de hormonas somatotrópica (STH) y tireotrópica (TTH) en ratas intactas y en tireoparatiroidectomizadas, nefrectomizadas unilateralmente y bebiendo NaCl al 1 por ciento.

STH en ratas intactas causa hipertensión, nefroesclerosis, poliuria, miocarditis e hipertrofia renal, cardiaca y suprarrenal. TTH en las mismas condiciones causa lesiones leves y hipertrofia renal y cardiaca, poliuria e hipertensión. En ratas tireoparatiroidectomizadas, todos estos efectos de la TTH están abolidos con excepción de una hipertrofia renal y cardiaca mínima. STH causa periarteritis nodosa y artritis, hipertrofia suprarrenal, cardiaca y renal leve y ligeras lesiones en el riñón. Las demás manifestaciones observadas en animales intactos están ausentes.

Se discute brevemente estos resultados.

Ann. rheum. Dis. (1955), **14**, 77.

ANKYLOSING SPONDYLITIS
A REVIEW OF 184 CASES

BY

F. DUDLEY HART

WITH AN APPENDIX BY

N. F. MACLAGAN

From the Westminster Medical School, London

(RECEIVED FOR PUBLICATION DECEMBER 22, 1954)

Some 5 years ago (Hart, Robinson, Allchin and Maclagan, 1949) we published a study of 73 patients with ankylosing spondylitis. In a follow-up study of these patients I have reviewed an additional 111 cases, personally examined, since that time. A study of these 184 patients (18 female, 166 male) forms the basis of this communication.

Symptomatology.—In this series of 184 cases the initial symptom was as follows:

Symptom	*No. of Cases*
Low backache	70
Low back stiffness without pain	18
Low back stiffness with slight pain	10
Buttock pains	21
Pain in "hips, groins or thigh"	16
Sciatica	9
Pain and/or swelling of knees	7
Pain and/or swelling of ankles, heels or feet	13
"Rheumatic fever"	4
Pyrexia of unknown origin with generalized aches and pains	2
Dorsal spine pain	6
Pains in shoulders	3
Head going forwards	2
Pains around the chest	3

Taking the first five headings together, 135 patients (73·4 per cent.) experienced pain and/or stiffness in the lower back and buttocks as the initial symptom as compared with 24 (13 per cent.) in whom the initial symptom lay in the periphery. The words "rheumatic fever" appear somewhere in the case history in eight instances in which it is clear that the disease was in fact ankylosing spondylitis.

In reviewing these case histories in detail it became clear that certain "small symptoms" were frequently present in the few months or years preceding the onset of the classical backache. If one accepted these early symptoms as part of the disease process, the age at onset ranged from 10 to 51 yrs in the male patients, and from 13 to 32 yrs in the female patients (Fig. 1). The discovery of sixteen

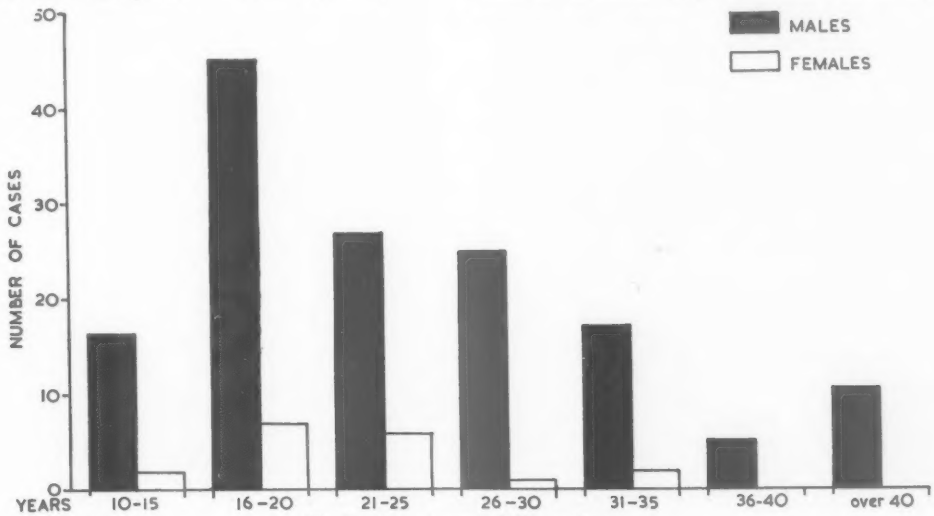


Fig. 1.—Age at onset of disease, by sex.

male patients in whom the early symptoms appeared between the ages of 10 and 15 years came as a surprise. It will be noted that 61 of these 184 patients developed the first symptoms of disease before their 21st birthday. Not infrequently complaints of intermittent "fibrositis" or occasional swelling of a peripheral joint marked the true onset of the disease. Such minor episodes appeared in the histories given by the patients at their first attendance and were not elicited by specific questioning; they appeared to be a part of this insidious relapsing-remitting disease rather than isolated and unconnected events. Three patients had made no complaint whatsoever and their spinal stiffness was discovered on routine examination. On closer questioning the typical history was forthcoming but the symptoms had been so slight that they had not been considered worthy of medical attention.

In four cases the initial pain assumed an erratic and peripheral course so that rheumatic fever was provisionally diagnosed. In two cases the acute, florid, extremely painful, clinical picture was seen, the patient being in too much pain to be out of bed but suffering extreme anguish at rest. The great majority presented in the usual manner, episodes of intermittent stiffness and aching in the back and buttocks gradually merging into the established disease pattern. Several secondary complaints were made later in the course of the disease. It is not intended to discuss these at length except to emphasize the frequency of bony tenderness, usually in the ischial tuberosities, but also in the brim of the pelvis, anterior superior iliac spines, greater trochanters, and occasionally sternum and ribs. This ischial tenderness may be a major complaint, usually lasting only a few weeks or months or occasionally much longer. One of these patients had carried a small protective cushion with him for the last 2 years.

One point of interest that has appeared worthy of note is the occurrence in the spondylitic of short quite severe painful episodes, often lasting only a few days or one or two weeks. Such episodes are usually self-terminating and the sufferer will refuse admission to a hospital bed, saying he will be better in a few days. No particular precipitating cause is evident, but pain and stiffness may exacerbate to a marked degree either in one segment or, less frequently, throughout the entire spine. Such short episodes are in no way comparable with the exacerbation of disease seen in rheumatoid arthritis. Trauma does not appear to be the cause.

Physical Signs.—The classical physical signs are well known and do not need to be mentioned here. In 43 of these 184 patients peripheral joint swelling occurred at some time in the course of the disease in the following order of frequency:

Site	*No. of Cases*
Knees	28
Ankles	21
Feet	11
Wrists	11
Fingers.. ..	8
Elbows ..	4

Measurement of Spinal Movement.—This can only properly be done by using an instrument which eliminates hip and leg movement. The usual mode of measuring spinal flexion by measuring the dis-

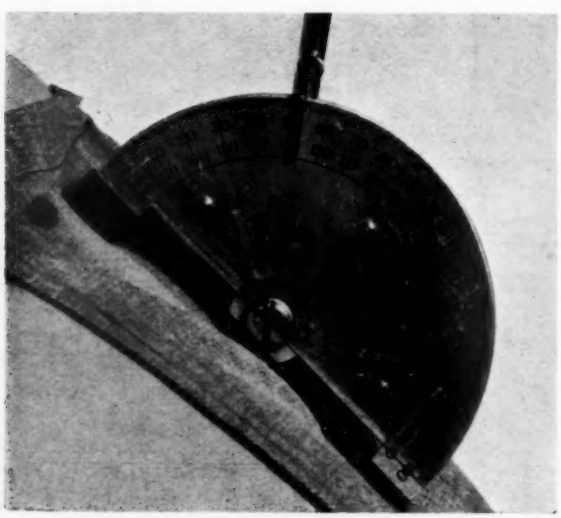


Fig. 2.—The Spondylometer.

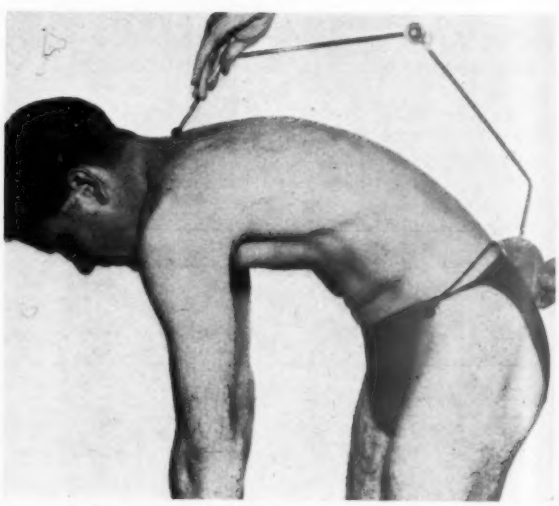


Fig. 3.—Measurement of spinal movement using the Spondylometer.

tance of the fingers from the floor with the spine in full flexion is notoriously unreliable as it measures not only spinal flexion but also hip mobility, pain and tenderness in hamstrings and knee and several other factors. For the past 4 years we have, therefore, been using a "Spondylometer", designed by Dr. W. F. Dunham (Figs 2 and 3; Dunham, 1949).

This instrument measures spinal movement between two points, the points we use being sacrum and vertebra prominens. Dunham has measured spinal movement in a number of normals and compared them with patients suffering from ankylosing spondylitis (Dunham, 1949). We have measured spinal range of movement in forty normal medical students, aged from 20-29 yrs, 5 ft. 5 in. to 6 ft. 3 in. tall. The spinal range lay between 75 and 120° and bore no relation to ability or inability to touch the floor with the fingers. No close parallel was observed between height and spinal range. These measurements are remarkably constant and provide the best measure of the progress of spinal stiffness in any given case. In early cases, where pain rather than structural change prevents movement, a definite increase can be obtained in the spinal range as a result of treatment by any effective method, whether it be cortisone, ACTH, or deep *x*-ray therapy, the response being much more rapid with the first two but less lasting (Hart, 1952). In most cases, however, there is a considerable degree of fixation of the spine and, though the pain may be greatly relieved by different forms of treatment, the spinal range of movement increases little, if at all. Fig. 4 illustrates spinal movement measured by the spondylometer in 143 patients at their first attendance at the clinic.

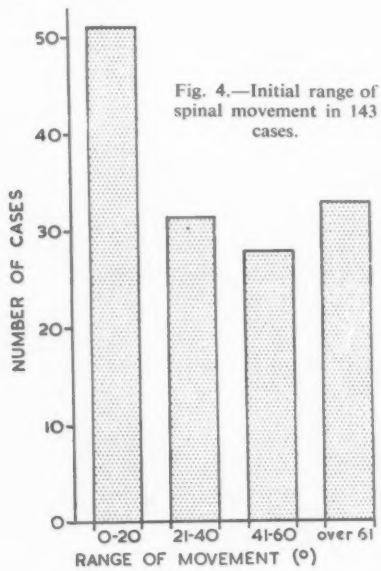


Fig. 4.—Initial range of spinal movement in 143 cases.

For the past 9 years we have, through the kindness of Dr. P. Hansell and the Photographic Department of the Westminster Hospital, taken clinical photographs of these patients (Fig. 5). Triple exposures illustrate certain points and serial photographs over the years enable one to record major changes in posture, but the method is not fine enough to use as a record of improvement or deterioration in posture or spinal mobility.

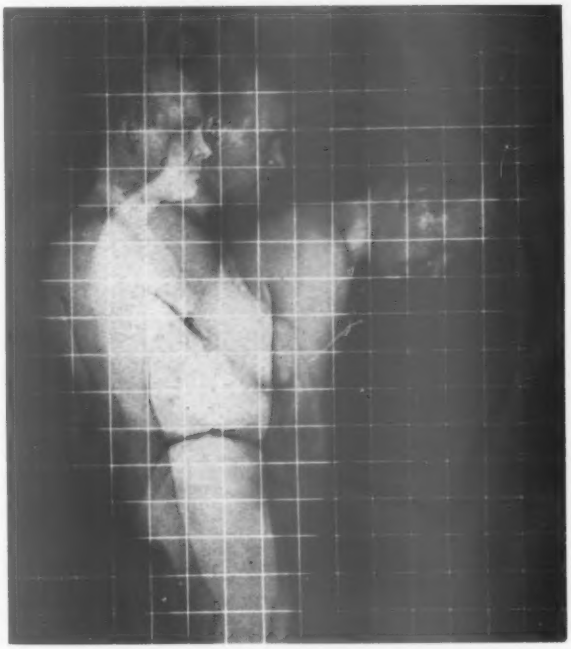


Fig. 5.—Triple exposure, showing range of spinal movement.

Thoracic Involvement.—A characteristic feature of ankylosing spondylitis is the reduced rib excursion which occurs as a result of fusion of rib with transverse process and body of vertebra. This reduction in intercostal respiration leads to over-use of the diaphragm and a double exposure skiagram of the chest in inspiration and expiration will, in such cases, demonstrate little rib movement but a generous diaphragmatic excursion (Hart, Bogdanovitch, and Nichol, 1950; Hart, 1950). The picture, therefore, differs from that seen in emphysema where both rib and diaphragm move little. This thoracic involvement is common in ankylosing spondylitis and though more frequent in advanced cases may occur as an early or even occasionally as a presenting physical sign. The resultant symptoms are usually stiffness of the chest wall, difficulty in fully expanding the chest, and an aching and discomfort on overbreathing, coughing, or sneezing. Tenderness and pain may also be felt in the sterno-manubrial region.

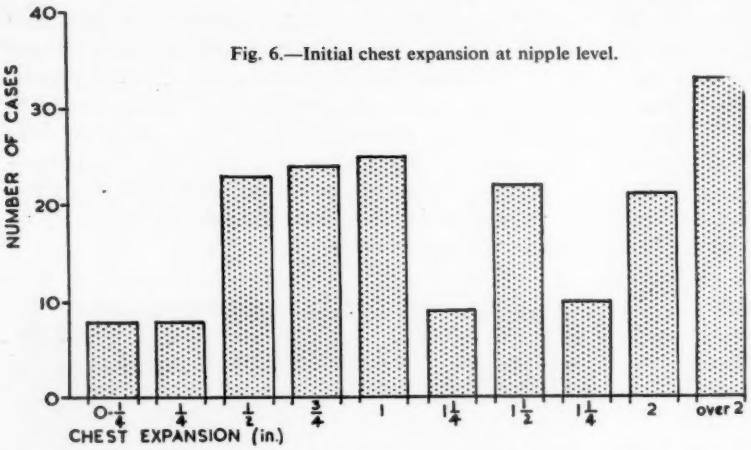


Fig. 6.—Initial chest expansion at nipple level.

In our series the initial chest expansion at nipple level, when first seen, was as follows (see also Fig. 6):

Expansion (in.)	*No. of Patients*	*Expansion (in.)*	*No. of Patients*
0	8	1¼	9
¼	8	1½	22
½	23	1¾	10
¾	24	2	21
1	25	Over 2	34

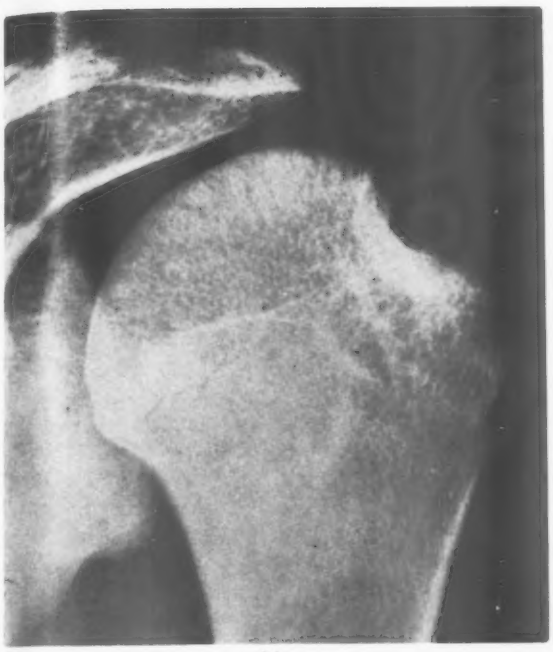
In 29 cases chest expansion was examined frequently over a period of 5 years or more; it improved, possibly as a result of therapy, in eighteen cases, was unchanged in five, and was worse in six.

Iritis and Iridocyclitis.—These ocular symptoms have long been recognized as more common in ankylosing spondylitis than in rheumatoid arthritis, but here again the length of the follow-up period will affect the results (Hart, 1951) and the incidence of 10 per cent. which is usually quoted, rises with an increase in the number of "observation years". Iritis may come on at any stage of the disease process and may also precede the spondylitis. In our series a history of iritis or iridocyclitis was forthcoming in 25 cases (13·5 per cent.). In one case iritis preceded spondylitis, in 24 cases it appeared at some time during the disease course, and in nine cases it occurred on more than one occasion. The incidence in our series will obviously rise with time.

Affection of the Sterno-Manubrial Joint.—This appears to be more common in ankylosing spondylitis than in rheumatoid arthritis. Savill (1951) found narrowing and eventual fusion of the joint in a high proportion of cases; 100 per cent. of spondylitics over the age of 35 showed abnormalities. Solovay and Gardner (1951) found fusion of the sterno-manubrial joint four times as common in ankylosing spondylitis (23 per cent. of cases) as in non-rheumatoid disease of the spine (5·5 per cent.). Françon and others (1953) state that though not uncommon, affection of this joint rarely gives rise to symptoms; where it does so injections of local anaesthetic may help. In our experience mild symptoms arising from involvement of this joint are by no means uncommon, tenderness on pressure, swelling, and pain being not infrequent complaints; though rarely persisting for more than a few weeks such symptoms may cause considerable discomfort.

Bony Tenderness.—As already stated, this may be a major complaint in ankylosing spondylitis, the common sites being the ischial tuberosities, pelvic brim, greater trochanters, and occasionally over the sacrum and vertebral spinal processes. Tenderness over the sternum and ribs is not uncommon. Such tenderness may constitute a major complaint and warrant local deep *x*-ray therapy to the affected part; *x*-ray changes are characteristic (Figs 7 and 8*a-d*). Tenderness in the heel may also be a sign of

Fig. 7.—Pelvic osteopathic changes in ankylosing spondylitis. Note absence of change on inner surface of pelvis.



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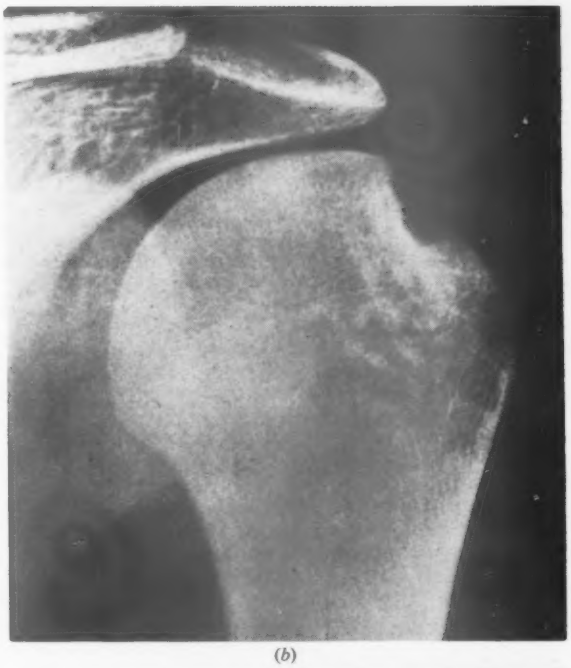

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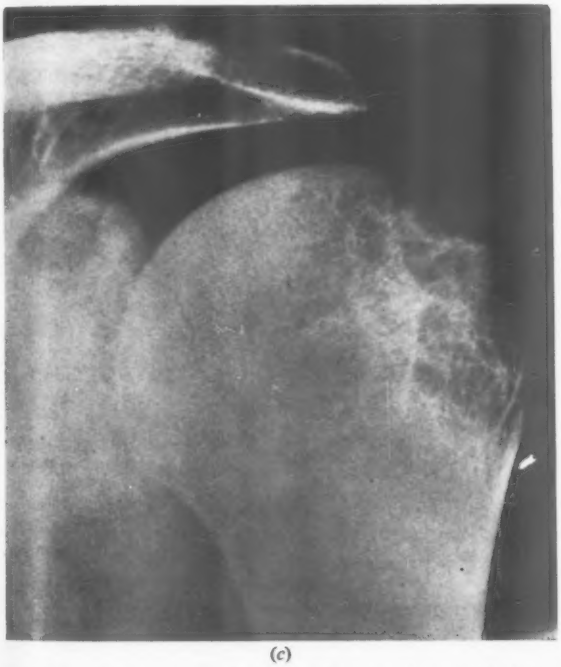

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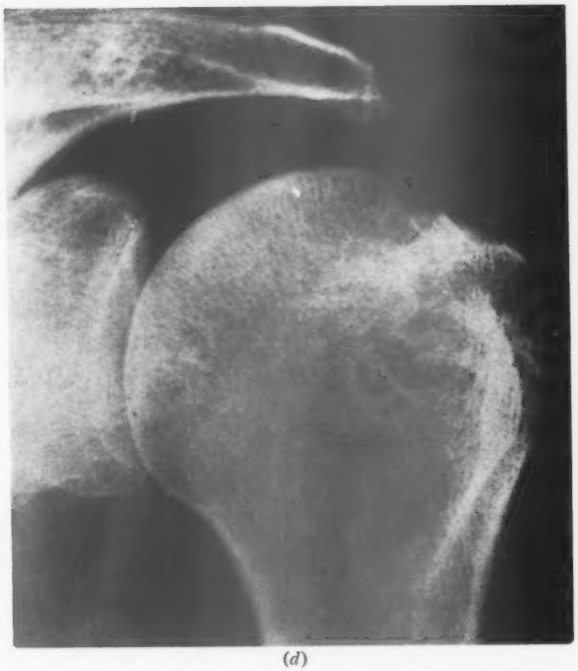

(*d*)

Fig. 8(*a*).—Bitten-out area in head of humerus in a classical spondylitic, who presented with acute pain in this area 24.9.49. All symptoms and signs disappeared in the subsequent five years, without local therapy.

Fig. 8(*b*). 18.4.50 Fig. 8(*c*). 5.6.51 Fig. 8(*d*). 3.5.54

ankylosing spondylitis; Davis and Blair (1950) state that males between the ages of 18 and 30 years with symptoms and signs of calcaneal periostitis or spurs should be suspected of having ankylosing spondylitis.

The diagnostic importance of these tender areas in bone is obvious. They are frequently misdiagnosed, commonly as tuberculous lesions, the resulting therapy—prolonged immobilization—producing unfortunate results. Ankylosing spondylitis

is a disease affecting bone as well as joint and ligament. It is an osteopathy as well as an arthritis; this is an important aspect of the disease which has often been overlooked.

Intercurrent Disease.—In these 184 patients, pulmonary tuberculosis with signs of activity was found in seven instances: in five the disease was parenchymal, whereas two presented with pleural effusion. Two further cases had quiescent disease and were merely kept under observation.

Dyspepsia of ulcer type was present without radiological abnormality in eight instances: six severe and two mild. Symptoms of a duodenal ulcer with a positive *x*-ray were found in seven instances: three had suffered from haematemesis or melaena, and one had perforated. A gastric ulcer was found on two occasions on barium meal examination, and also one case of carcinoma of the stomach. Melaena occurred once during phenylbutazone therapy, and twice during deep *x*-ray therapy, in both instances where a course of 2,000r was being administered to all ports. In all, therefore, 21 patients showed some evidence of peptic ulceration, three being associated with some form of therapy and 10 with radiological abnormality.

Summary

(1) In surveying the case histories of 184 patients with ankylosing spondylitis the onset of symptoms was found to have occurred before the age of 21 in 61 cases. Minor symptoms in peripheral joints may precede pain and stiffness in the back by months or years. In 24 cases (13 per cent.) pain and/or swelling of peripheral joints was the initial symptom. Four cases were misdiagnosed as rheumatic fever.

(2) Measurement of spinal movement is discussed. The "spondylometer" of Dr. W. F. Dunham has proved extremely useful.

(3) Of 184 patients, 88 had a chest expansion of 1 in. or less at nipple level at their initial attendance.

(4) Iridocyclitis was present in 25 instances (13·5 per cent.), active pulmonary tuberculous disease was noted in seven cases, and some evidence of peptic ulceration in 21 cases.

(5) The serum proteins and flocculation tests are recorded in 86 cases (see Appendix). The albumin was low, the globulin and fibrinogen were high, and the flocculation tests were positive in a proportion of cases. The changes were similar to those seen in rheumatoid arthritis but smaller in extent.

Our thanks are due to Dr. Peter Hansell of the Department of Medical Photography, Westminster Medical School.

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Spondylite ankylosante

RÉSUMÉ

(1) L'analyse des observations de 184 malades atteints de spondylite ankylosante montre que dans 61 cas les premiers symptômes ont débuté avant l'âge de 21 ans. Des mois et des années peuvent s'écouler entre le début des symptômes mineurs dans les articulations périphériques et l'apparición de la douleur et de la rigidité dorsale. Dans 24 cas (13%) la douleur et tuméfaction des articulations périphériques furent des symptômes initiaux. Chez quatre malades on fit le diagnostic erroné de rhumatisme articulaire aigu.

(2) On discute la mesure du mouvement vertébral. Le "spondylomètre" du Dr. W. F. Dunham s'est montré extrêmement utile.

(3) Au premier examen, l'ampliation thoracique au niveau du mamelon fut inférieure à 26 mm. chez 88 malades sur 184.

(4) L'iridocyclite fut présente dans 25 cas (13,5%), la tuberculose pulmonaire active dans 7 cas et dans 21 cas on observa des signes d'ulcération peptique.

(5) Les taux des protéines sériques et les résultats des réactions de floculation furent notés dans 86 cas. Les taux d'albumine furent bas, ceux de la globuline et du fibrinogène élevés et les réactions de floculation positives dans un certain nombre des cas. Les lésions furent similaires à celles observées dans l'artrite rhumatismale mais de moindre envergure.

Espondilitis anquilosante

SUMARIO

(1) El análisis de 184 observaciones de enfermos con espondilitis anquilosante muestra que en 61 casos los primeros síntomas presentáronse antes de la edad de 21 años. Síntomas menores en articulaciones periféricas puden preceder de meses y hasta de años el dolor y la rigidez dorsal. En 24 casos (13%) el dolor e hinchazón de las articulaciones periféricas fueron síntomas iniciales. En cuatro enfermos se hizo el diagnóstico erróneo de reumatismo poliarticular agudo.

(2) Se discute la medición del movimiento vertebral. El "espondilometro" del Dr. W. F. Dunham mostrose muy útil.

(3) Al examen inicial la ampliación torácica al nivel del pezón fué inferior a 26 mm. en 88 enfermos sobre los 184.

(4) La presencia de iridociclitis fué notada en 25 casos (13,5%), de tuberculosis pulmonar activa en 7 casos e indicios de ulceración péptica observáronse en 21 casos.

(5) Las cifras de las proteinas séricas y los resultados de las reacciones de floculación fueron notados en 86 casos. Las cifras de albumina fueron bajas, las de globulina y de fibrinógeno altas y reacciones de floculación positivas en un número determinado de los casos. Las alteraciones patológicas fueron similares a las observadas en la artritis reumatoide pero no tan extensas.

APPENDIX

LABORATORY INVESTIGATIONS

BY

N. F. MACLAGAN

Serum Proteins

These were estimated in some seventy patients with ankylosing spondylitis attending Westminster Hospital during the period 1950-52. 22 per cent. weight in volume sodium sulphate was used for precipitating the globulins and the standard micro-kjeldahl procedure was adopted. The results are shown in Table I; 21·2 per cent. of the cases had low albumin values while 33·2 per cent. had raised globulin values. The albumin/globulin ratio was below normal in 37·1 per cent. The plasma fibrinogen was also estimated in 38 patients with this condition, and 34·2 per cent. of these gave abnormally high results.

These figures differ fairly markedly from normal values, the deviation being in the same direction as that seen in rheumatoid arthritis. A parallel series of cases of rheumatoid arthritis investigated at the same time showed, however, a significantly greater deviation from the normal in the case of the albumin, globulin, and albumin/globulin ratio, but a rather smaller increase in the fibrinogen results (16 per cent. of cases abnormal).

The results as a whole indicate a considerable upset of protein metabolism in spondylitis of the same type frequently associated with severe chronic infections.

Flocculation Tests

These were performed on a series of 86 cases with the results shown in Table II. All the flocculation tests tried showed a considerable percentage of positive results, the maximum occurring with the ammonium sulphate test (33 per cent.) and the minimum with the thymol turbidity and flocculation tests (11·6 and 12·8 per cent.). For technical reasons the serum colloidal gold test is to be preferred for demonstrating this type of change in rheumatic conditions; this gave 23·2 per cent. positive.

These figures, while showing a significant deviation from normal, are not so impressive as those obtained in rheumatoid arthritis, which in a parallel series of cases gave positive results ranging from 49·6 per cent. with the colloidal gold reaction to 26·7 per cent. with the thymol turbidity test.

As with the serum proteins, the changes are similar to those found in severe chronic infections and appear to be non-specific in character. It is possible that they depend partly on disturbance of liver function, but this is as yet unproved.

APPENDIX TABLE I
PLASMA PROTEINS IN SPONDYLITIS

Fraction	Normal Limits (g/100 ml.)	No. of Cases	Mean ± SE (g./100 ml.)	Per cent. Abnormal
Albumin	4·0–5·5	66	4·321±0·074	21·2
Globulin	1·5–3·0	66	2·617±0·099	33·3
Fibrinogen	0·2–0·5	38	0·446±0·026	34·2
A/G Ratio	1·5–2·5	66	1·81 ±0·086	37·1

APPENDIX TABLE II
FLOCCULATION TESTS IN SPONDYLITIS

Test	Method	Normal Limits	No. of Cases	Mean ± SE (units)	Per cent. Abnormal
Ammonium Sulphate ..	Huerga and others (1950)	0–2	18	2·25 ±0·038	33·3
Zinc Sulphate	Kunkel (1947)	0–4	65	3·190±0·29	16·9
Serum Colloidal Gold ..	Maclagan (1944a)	0	86	0·44 ±0·11	23·2
Thymol Turbidity	Maclagan (1944b)	0–2	86	1·48 ±0·13	11·6
Thymol Flocculation ..	Maclagan (1947)	0	86	0·15 ±0·45	12·8

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THERAPY OF "FELTY'S SYNDROME"

BY

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(RECEIVED FOR PUBLICATION AUGUST 19, 1954)

The incidence of normocytic hypochromic anaemia in rheumatoid disease is very high (Nilsson, 1948; Empire Rheumatism Council Scientific Advisory Committee, 1950; Jeffrey, 1952); while its aetiology is obscure, its severity appears to fluctuate with exacerbations of joint swellings (Kahlmeter, 1922; Nilsson, 1948). Occasionally the anaemia has the additional feature of a severe leucopenia, and if this becomes associated with progressive arthritis and splenomegaly, as was first noted by Chauffard and Ramond (1896), the clinical syndrome described by Felty (1924) emerges. This symptom complex is comparatively rare and has only been seen three times in this unit during the last 3 years. The reports in the literature of "Felty's syndrome" similarly comprise only small series (Singer and Levy, 1936; Edström, 1941; Talkov, Bauer, and Short, 1942; Trolle and Trolle, 1943; Dameshek, 1944; Hatch, 1945; Hirschboek, 1946; Nyström, 1946; Cole, Walter, and Limarzi, 1949; Hutt, Richardson, and Staffurth, 1951).

The duration of the rheumatoid disease and the onset of the clinical manifestations of "Felty's syndrome" are not significantly related. Hutt and others (1951) reported four cases in which the time interval varied between 7 and 29 years. Similarly no specific age incidence was found by these authors. A predominance of this syndrome in females is noted, but rheumatoid disease is usually more common in women.

Certain unusual clinical manifestations encountered in the course of rheumatoid disease suggest the possible presence of "Felty's syndrome". Refractory anaemia, recurrent disabling infections, and buccal and other mucosal ulcerations may suggest pancytopenia or agranulocytosis in view of the numerous drugs used in the management of rheumatoid disease. The agranulocytosis may be cyclical and associated with splenomegaly (Löffler and Maier, 1947). Hutt and others (1951) recorded two cases of "Felty's syndrome" presenting corneal ulceration, and one with ulceration of the legs. They also referred to the records of two other patients in their hospital who apparently suffered from severe keratitis.

In patients with "Felty's syndrome", leucopenia is associated with splenomegaly and normal maturation of granulocytes in the bone marrow, unlike agranulocytosis. Marrow hypoplasia with leucopenia which improved with splenectomy was, however, observed by Rogers and Langley (1950). The peripheral blood findings are variable, but a severe granulopenia with total white cell counts varying from 800 to 3,500 was noted by Hutt and others (1951). Thrombocytopenia is not uncommon, and haemorrhagic features were reported by Dameshek (1944).

Present Investigations

This paper records the clinical management of three cases of this syndrome.

Case 1, a male aged 49, gave a history of rheumatoid disease affecting the left knee and both wrists for the past 10 years. He had also had psoriasis for many years. More recently he had developed progressive diarrhoea which occasionally contained blood. On examination, the most striking findings, apart from the joint lesions, were splenomegaly, anaemia, and leucopenia. Sigmoidoscopy did not reveal any abnormality in the colon.

The diagnosis of "Felty's syndrome" was made and whole blood was given in preparation for splenectomy. The clinical course of this patient before splenectomy was dominated by neutropenia which persisted in spite of transfusion and necessitated operation (Fig. 1, opposite). L.E. cells were not found.

Operation.—An enlarged but otherwise normal spleen was removed.

Effects of Splenectomy.—Splenectomy controlled the anaemia (one year later the haemoglobin was 13 g. per cent.), no further blood transfusions were required and the leucocytes rose to 16,000 per c.mm. on the 16th postoperative day. They gradually fell and a moderate leucocytosis persisted for a year. With the restoration of the patient's white cell count his general health improved and his arthritis remitted.

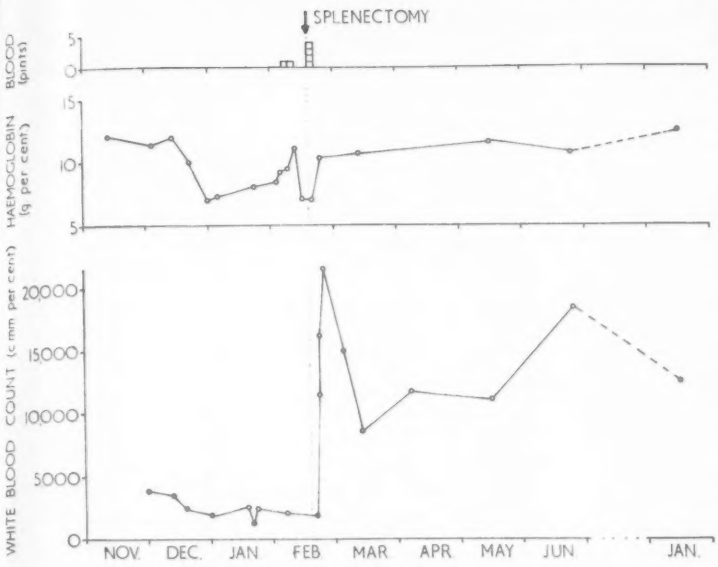

Fig. 1.—Case 1.

Case 2, a female aged 66, gave a history of severe pain and swelling of the elbows, wrists, proximal interphalangeal joints, and knees for the past 6 years. There had been much loss of weight. Typical rheumatoid changes were found in both elbows, wrists, and knees, and in all proximal interphalangeal joints; an old congenital dislocation of the left hip joint was also present. Emaciation, splenomegaly, neutropenia, and anaemia were the other findings of note.

In spite of whole blood transfusion and intravenous iron, improvement in the anaemia and white cell count was only temporary. The marrow was cellular and micronormoblastic. A weakly positive occult blood test on the stool was not considered a suitable explanation for the persistent fall of haemoglobin. Haemolysis could not be excluded, but the survival time of transfused red cells appeared to be normal over a period of 14 days.

In an attempt to stem her downhill course and prepare her for splenectomy a short course of 900 mg. ACTH and multiple transfusions were given over a period of 9 days, during which the white cell count remained unchanged and the haemoglobin showed only a slight rise—probably due to transfusion (Fig. 2).

While clinically the diagnosis was apparent at the time of her out-patient attendance, her general condition, and particularly the refractory anaemia, created many obstacles before splenectomy could be contemplated. Liver palms, spidery naevi, enlarged abdominal veins (seen by infrared photography), and oesophageal varices suggested additional liver disease with portal hypertension. During a liver biopsy the liver felt hard and was penetrated with some difficulty, but the piece of liver obtained appeared normal. Liver function tests showed parenchymal liver damage.

Operation.—The liver appeared to be fibrotic. The biopsy macroscopically suggested cirrhosis, but microscopically there was some increase in periportal fibrous tissue only and moderate infiltration of the portal tracts with lymphocytes.

The spleen was enlarged, its surface was mottled, and some adhesions were present. The cut surface showed an indistinct pattern with some fibrosis of the pulp. Histological examination showed fibrosis of the sinusoids with scanty infiltration by histiocytes, some plasma cells and lymphocytes, and scanty eosinophils. The Malpighian bodies were small and atrophic. Frequent foci of fibrosis and haemosiderin-laden macrophages were noted.

Post-Operative Course.—Following splenectomy this patient's haemoglobin rose to 11 g. per cent., the white cells to 8,000 per c.mm., and the platelets to 220,000 per c.mm.; 50 days later the haemoglobin began to fall and the rheumatoid arthritis became active again. She was then given a second course of ACTH totalling 700 mg. over 7 days; this was followed 12 days later by another course of 750 mg. lasting 10 days. While the patient improved subjectively, there was no immediate significant change in the blood picture. It is of interest, however, that less than a month after the cessation of

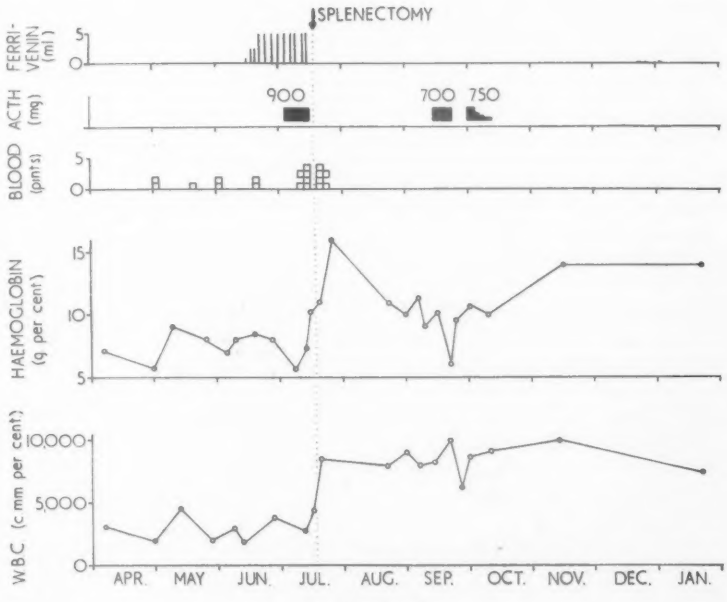

Fig. 2.—Case 2.

ACTH both the haemoglobin and the white blood count rose rapidly to 14 g. per cent. and 10,000 per c.mm. respectively without further need of specific therapy, and these levels were maintained for 6 months until the patient's death (Fig. 2). While the plasma proteins showed little change, some deterioration in liver function tests suggested progressive liver disease. Subjectively the patient was markedly improved and able to walk once more after many years of crippledom, but she succumbed, 6 months later, with a pontine haemorrhage.

Case 3, a female aged 57, suffered from rheumatoid disease for 14 years which affected principally the elbows, wrists, metacarpo-phalangeal joints, and the right knee. At the time of admission she was emaciated and had multiple septic lesions affecting the skin over the left external malleolus, right great toe, and right tibia. Melaena was also present.

On examination signs of rheumatoid involvement of the aforementioned joints were seen and splenomegaly was noted. Severe anaemia, leucopenia, and thrombocytopenia were found. Sigmoidoscopy showed mucosal oozing only. The melaena demanded rapid transfusion and 8 pints of blood were given without immediate improvement. However, after a further 4 pints of blood the melaena ceased. As the peripheral blood was megalocytic, a sternal marrow puncture was carried out, which showed marked megaloblastic degeneration of the marrow. Vitamin B_{12} was then given in doses of 200 μg. weekly for 2 weeks, and then 300 μg. weekly for a further 2 weeks. The failure of the red cell count to rise in the presence of a reticulocytosis of 15 per cent. excluded a typical pernicious anaemia (achlorhydria was present). No evidence of haemolysis was found, the serum bilirubin excretion were normal, and the direct Coombs test was negative. While she was receiving vitamin B_{12}, the platelet count rose from 75,000 to 144,000 per c.mm., but the total white cell count remained at the level attained by transfusion alone (between 3,000 and 4,000 per c.mm.). The marrow, however, reverted to normoblastic and remained so for about 4 months after cessation of B_{12} therapy. An interesting feature was the presence of giant multinucleated megaloblasts in the earlier films and normoblasts in subsequent films. This feature persisted throughout the period of observation. L.E. cells were not found.

While the haemoglobin increased by 3 g. (from 9 to 12) per cent. and the platelets increased from 75,000 to 144,000 per c.mm. during B_{12} therapy, the total white cell count was uninfluenced.

After 4 weeks of continuous B_{12} therapy it was found that the leucocytes remained at a level between 3,000 and 4,000 per c.mm. (with the exception of one short interval), and similarly the haemoglobin level remained between 9 and 10 g. per cent. 920 mg. ACTH were then given over a period of 13 days; this caused the haemoglobin to rise from 10 g. to 11·8 g. per cent., the white cells from 3,000 to 6,100 per c.mm., and the platelets from 110,000 to 180,000 per c.mm. The reticulocytes, formerly about 2 per cent., rose to 5 per cent. These levels did not persist and were only reached again after splenectomy, which was carried out to prevent renewed leucopenia after cessation of ACTH. This, in fact, was probable as the white cells fell again just before splenectomy (Fig. 3, opposite). The patient's liver function tests were as follows:

Total serum protein	..	4·8 per cent.
Albumin	..	2·8 per cent.
Globulin	..	2·0 per cent.
A/G ratio	..	1·4
Serum bilirubin	..	0·6 mg. per cent.
Zinc turbidity	..	4·5 units
Thymol turbidity	..	4 units
Alkaline phosphatase	..	4·2 units (King-Armstrong)

The increased urinary urobilinogen suggested the possibility of portal hypertension and cirrhosis, but a pre-operative punch biopsy of the liver was normal.

Operation.—An enlarged but otherwise normal liver was found; and histological examination showed slight focal fatty change of the parenchymal cells only. The spleen weighed 570 g. Its capsule was smooth with an occasional area of perisplenitis and fibrinous exudate. The cut surface was uniformly red with distinct, small, and widely-scattered Malphigian bodies. Histologically the pulp showed some fibrosis and considerable infiltration by histiocytes, lymphocytes, plasma cells, and eosinophils. The Malphigian bodies were large and contained prominent germinal centres.

Post-Operative Course.—Splenectomy had no effect on the haemoglobin level; the leucocytes, formerly never above 8,200 per c.mm., after splenectomy and during a mild post-operative infection, rose to 17,800 per c.mm. The platelets, 180,000 per c.mm. pre-operatively, rose to 300,000 per c.mm. post-operatively, falling later to 233,000.

The marrow remained normoblastic for 4 months when macronormoblastic change was seen. Although it was difficult to see why there should have been a deficiency of folic acid, the diet and fat balance (28 g. total fat per 100 g. dried faeces) being normal, 10 mg. folic acid were given daily; in spite of a reticulocytosis of 8 per cent., however, there was no significant change in the total red cell count and haemoglobin. One month after beginning folic acid therapy the marrow was found to be normoblastic.

The liver function tests showed some further deterioration. The total plasma proteins rose with the improvement in the anaemia, but the A/G ratio deteriorated as did the parenchymal liver function tests. Splenectomy did not bring about any change in the reticulocytes.

The general condition improved after operation, and the patient was able to go to a convalescent home as an ambulant and self-sufficient person. Here for 4 months her condition was satisfactory and improvement continued. Death, however, occurred after a short acute illness.

Post-mortem Examination.—An acute fibrinous pericarditis was found, the pericardial sac containing some yellowish-green pus, and the visceral pericardium showing some irregular patches of yellow deposit which were

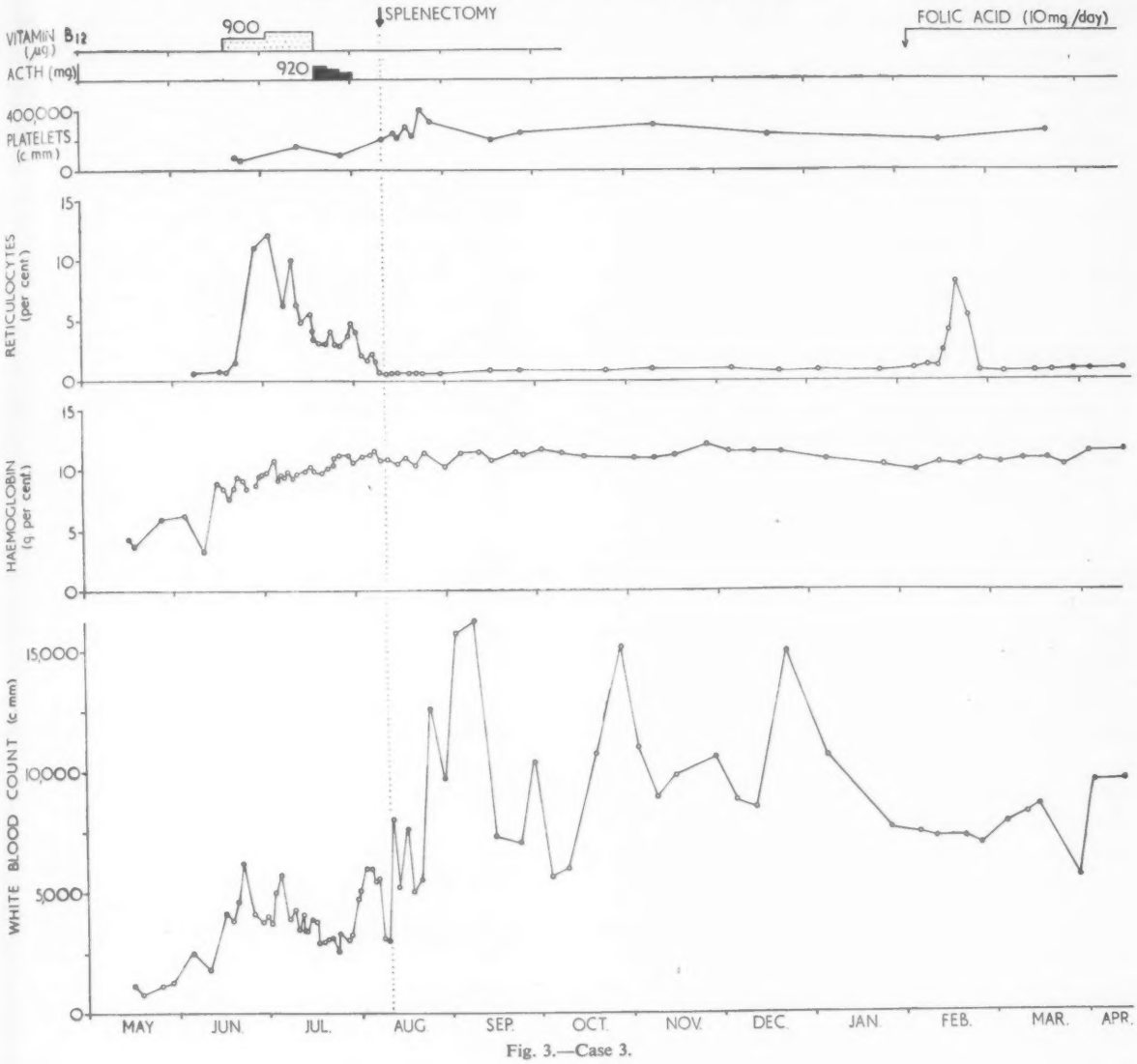

Fig. 3.—Case 3.

almost crystalline in appearance. Histological examination showed non-specific inflammatory changes only, and culture of the pus grew a few coliform bacilli.

The only other significant finding was an enlargement of the aortic lymph nodes which were red in colour; histological examination showed active haemopoiesis. Three small spleniculi (together weighing 5 g.) were present in the splenic bed; histologically these were essentially the same as the spleen removed at operation. The liver was enlarged (2,286 g.) and mottled; histological examination showed some fibrosis and chronic inflammatory cell infiltration of the portal tracts and zonal necrosis of the parenchyma consistent with congestive cardiac failure. A small collection of pus, which grew coagulase positive *Staph. pyogenes*, was present in the middle cranial fossa. A healed subchronic gastric ulcer was present in the pyloric canal.

Discussion

The experience gained from these three cases counsels splenectomy as the only therapy so far known to arrest the blood dyscrasia and restore the peripheral blood picture in "Felty's syndrome".

In Cases 1 and 2 agranulocytosis was excluded by marrow puncture. In Case 3 the marrow was megaloblastic but did not show a primary defect of granulopoiesis. After the marrow reverted to normoblastic following B_{12} therapy, the total number of white cells in the peripheral blood stayed low until after splenectomy. The granulopenia seen in this disease cannot, therefore, be attributed to faulty granulopoiesis and its cause should probably be sought in the concomitant hypersplenism.

Case 3 presented with a pancytopenia, not unlike that described by Doan and Wright (1946), who thought that this was a manifestation of "splenic overaction". The assumption that hypersplenism was responsible for the blood changes in our three cases is probably correct, particularly as the peripheral blood reverted to nearly normal after splenectomy.

We have no explanation to offer regarding the precise mechanism of hypersplenism in "Felty's syndrome". Hirschboeck (1946) discusses two explanations of the accompanying phenomena: the one suggests that the bone marrow may become inhibited by some hormonal factor related to the enlarged spleen, the other that leucopenia results from increased splenic phagocytosis (Wiseman and Doan, 1939).

The possibility that these cases might well be variant patterns of disseminated lupus erythematosus had been considered, but the absence of cutaneous, visceral, and urinary manifestations, and the failure to find L.E. cells in Cases 1 and 3 made this diagnosis improbable. The response to ACTH was poor, and splenectomy became imperative in order to arrest further clinical deterioration.

The possibility that haemolysis plays a part in these cases has not been excluded. The anaemia associated with rheumatoid disease constitutes a separate problem, but Jeffrey (1952) found no haemolysis in anaemic patients with rheumatoid arthritis. Nilsson (1948) thought that disturbances in haemoglobin synthesis resulted from failure of iron utilization and absorption, and he found it rare for serum iron to be above 35 μg. even after intravenous iron. It is improbable that in "Felty's syndrome" a primary defect of haemoglobin synthesis is solely responsible for the anaemia, which probably also has a haemolytic element. This latter possibility was borne out in our cases by the rapid relapse of the anaemia after massive transfusions.

The aetiology of portal hypertension in "Felty's syndrome" remains obscure. Hepatosplenomegaly is a not uncommon finding in rheumatoid disease, and Schlesinger (1949) found it present in 50 per cent. of his series of cases of Still's disease. It can thus be regarded as part of the rheumatoid process, although not associated with any specific pathological appearances.

Splenic enlargement is often associated with portal hypertension, but "hypersplenism" is unusual in simple portal hypertension and it would appear that hypersplenism may be the end result of reticulo-endothelial hyperplasia consequent upon a very chronic inflammatory condition, in this case rheumatoid disease.

That progressive liver damage was in fact taking place is evidenced by the deterioration of liver function in Case 2, and it was to be expected in Case 3 as portal hypertension was evidenced by distended abdominal veins and oesophageal varices. It is unfortunate that two of our cases have died. The cause of death in Case 2 was probably unrelated to her rheumatoid disease, but in Case 3 the acute pericarditis was clearly the immediate cause of death. This was not found to be bacterial in origin, and, although of non-specific inflammatory type, is probably rheumatoid in origin. Pericarditis is a recognized complication of rheumatoid disease (Ellman, Cudkowicz, and Elwood, 1954).

Hanrahan and Miller (1932) reported satisfactory improvement both in the blood picture and in the joint manifestations following splenectomy. It appears to us that splenectomy is still the treatment of choice to be carried out as soon as the patients are fit enough for surgery. The subjective improvements in the joints in our three patients developed gradually; they were not directly related to splenectomy but occurred as soon as the general health improved. The use of iron, vitamin B_{12}, folic acid, hormones, and blood transfusion can only be regarded as ancillary aids; in Case 2 transfusion alone was by far the most important single form of therapy permitting the patient to come to surgery.

Summary

Three cases of "Felty's syndrome" are described. Of the various forms of therapy tried blood transfusion was found to be the most important ancillary aid, but only splenectomy gave any degree of immediate relief.

The pathogenesis of the condition is briefly discussed.

We are indebted to Dr. J. V. Dacie of the Department of Haematology, Post-Graduate School of Medicine, London, for his valuable help in connexion with Case 3; to Dr. A. Dolphin, Consultant Physician to Mile End Hospital, for permitting us to include Case 1, seen repeatedly by one of us (P.E.) in consultation; and to Dr. A. G. Signy, Director of the Group Laboratory, St. Mary Abbott's Hospital, London, for his help in the pathological sphere.

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Traitement du syndrome de Felty

RÉSUMÉ

On décrit trois cas de syndrome de Felty. Parmi toutes les formes de traitement essayées, la transfusion sanguine s'est montré le remède adjuvant le plus important, mais la splenectomie seule produisait un soulagement immédiat appréciable.

On discute brèvement la pathogénie de cet état.

Terapia del síndrome de Felty

SUMARIO

Se describe tres casos de síndrome de Felty. De todas las formas de tratamiento ensayadas, la trasfusión de sangre reveló su suma importancia como remedio coadyuvante, mas la esplenectomia sola produjo un alivio inmediato apreciable.

Se discute brevemente la patogenesis de esta condición.

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A SIMPLE POSTURE METER

BY

R. HARRIS

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(RECEIVED FOR PUBLICATION SEPTEMBER 27, 1954)

In ankylosing spondylitis a simple method of measuring and recording spinal deformity is of value in assessing progress. Methods in use include serial photography, serial strip plaster-of-paris casts, and lead-moulding tracing the outline on to paper.

The apparatus described below is cheaper, less cumbersome, and more simple and convenient to use.

Construction

It consists of an upright, 6 ft. 3 in. high, mounted on a wooden base (Fig. 1). The upright is made of 3-in. × 2-in. wood, and has fourteen horizontal holes bored through it, of 3/16-in. diameter, the centres being 3 in. apart. Through these closely fit cylindrical wooden rods, graduated in half inches. The rods vary in length, so that the longest projects 18 in. from the upright. Convenient projection lengths are five of 18 in., five of 10 in., and four of 6 in. Rubber caps at either end prevent displacement of the rods. Heel holds are fitted to the base.

Method of Use

The subject stands on the platform with his heels in the heel holds and back to the upright, and adopts his best posture. The rods are pushed through to press against the vertebral column and back of the head. The patient then steps off the platform, the distance by which each rod protrudes is noted, and the "spinal profile" is plotted on graph paper. Although this graph does not entirely exclude knee and hip deformity it provides a useful record of the patient's best standing position.

Application

The chart of an improving case of ankylosing spondylitis (Fig. 2) shows how easily progress can be assessed, without having to rely on clinical memory or elaborate records. The area between the profile and the upright gives an approximate estimate of the total deformity.

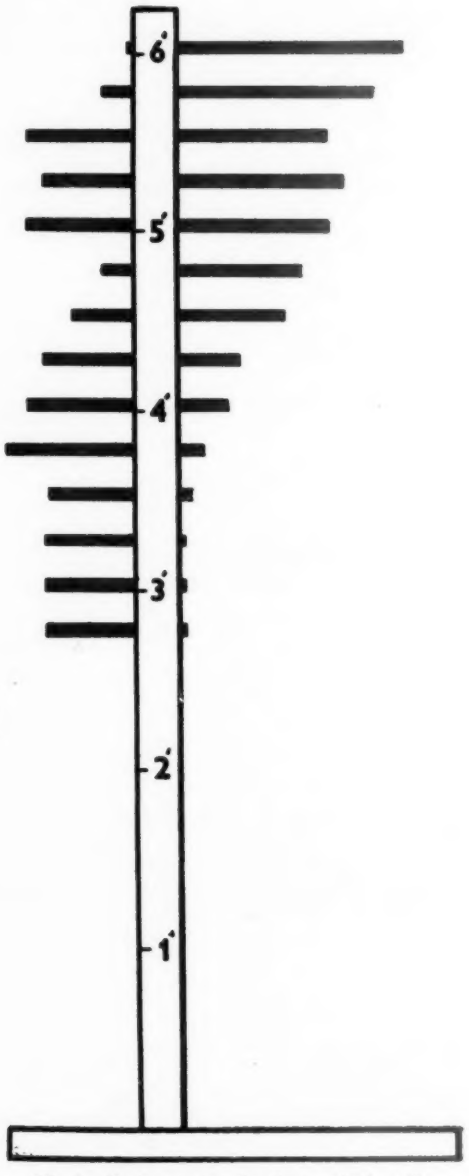

Fig. 1.—Posture meter, showing a spinal profile.

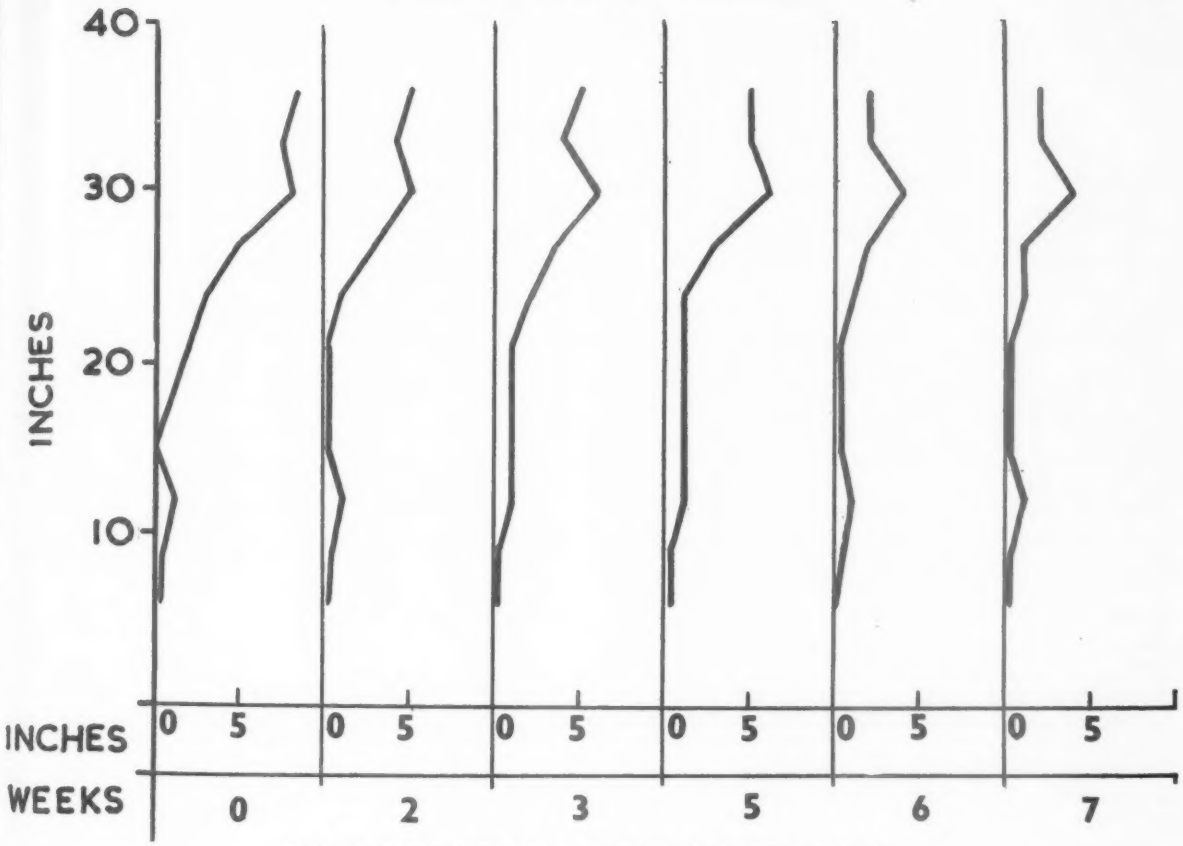

Fig. 2.—Serial recordings of an improving case of ankylosing spondylitis.

Un simple appareil à mesurer la posture

RÉSUMÉ

On décrit un nouvel appareil qui permet de mesurer et enregistrer la difformité vertébrale dans la spondylite ankylosante. Il consiste d'un montant de plus de six pieds de hauteur sur une base pourvue de niches pour les talons. Ce montant est percé en ligne verticale de 14 trous équidistants traversés de barreaux mobiles et gradués. Le malade monte sur la base, le dos au montant, et adopte sa meilleure posture. On pousse alors les barreaux de manière qu'ils touchent l'épine et on note leur distance du montant. Cela permet une reconstruction graphique rapide et fidèle de la courbure vertébrale. On peut également déterminer la surface entre les lignes du montant et de la colonne et le chiffre obtenu peut servir d'indice de la difformité.

Un aparato simple para medir la postura

SUMARIO

Se describo un aparato que permite medir y registrar la deformación vertebral en la espondylartritis anquilozante. Consiste de un montante de más de seis pies de altura, atravesado en línea recta de 14 varillas equidistantes, graduadas y móviles. El enfermo sube a la base del montante, pone los talones en los nichos provistos para ello y, con la espalda hacia el montante, adopta su mejor postura. Se empuja entonces las varillas para que toquen la espina y se nota la distancia del montante. Esto permite la reconstrucción gráfica rápida y fiel de la curvatura vertebral. Se puede también determinar la superficie comprendida entre la línea del montante y la de la espina y la cifra obtenida puede servir como indicio de la deformación.

BOOK REVIEWS

Textbook of the Rheumatic Diseases. Edited by W. S. C. Copeman. 2nd edition, 1955. Pp. 754, 349 figs (11 in colour). Livingstone, Edinburgh. (52*s.* 6*d.*)

The second edition of this well-known textbook comes well up to the high standard set by the first. The editor is to be congratulated again on the choice of his 26 contributors, for they include such authorities as Lord Horder and Dr. E. G. L. Bywaters who write on rheumatic fever, Sir Henry Cohen who writes two most stimulating chapters on gout and the rarer arthropathies, Sir Stanley Davidson and Dr. J. J. R. Duthie on rheumatoid arthritis, and Professor J. H. Kellgren on pain, to mention only a few. A work of multiple authorship of this kind is bound to show certain irregularities, and different sections are bound to overlap to some extent, but on the whole the balance is very well preserved and the work is extremely even. Professor D. V. Davies has a chapter on anatomy and physiology of the joints, Dr. L. G. C. Pugh on physical environment and rheumatic disease, Dr. Bernard Schlesinger on Still's disease, Sir Reginald Watson-Jones and Mr. Osmond-Clarke on orthopaedic treatment—each aspect is covered very adequately by a well-recognized authority on his subject.

Only few criticisms can be made. A chapter on the so-called "para-rheumatic" disorders (disseminated lupus erythematosus, scleroderma, polyarteritis nodosa) could conveniently be considered for the next edition, for Dr. Oswald Savage, in an excellent chapter on the adrenal hormones, is the only author to discuss them in any detail. References to important written work in this expanding and active field of medicine should be given at the end of every chapter and not only after some, for the serious student of the subject, having sipped, might perhaps often wish to drink deeper; it would also make for a more even work if a common practice obtained throughout the book.

The second edition of this book is dedicated, by permission, as was the first, to H.R.H. the Duke of Gloucester, K.G., F.R.S., President of the Empire Rheumatism Council. It is fully worthy of this honour.

F. Dudley Hart.

Rheumatism. By W. S. C. Copeman and R. M. Mason. 1954. Modern Health Series: Duckworth, London. (8*s.* 6*d.*)

This small book is written for the patient suffering from rheumatic disease. It is packed with sound advice and authoritative statements on the value of different forms of treatment. The rheumatic diseases are discussed in turn and placed in sensible perspective which should clear up for the layman certain misunderstood features of "rheumatism". It is pointed out that "fibrositis" is still a convenient term for a number of conditions of unknown causation. The various other names used to designate localized soft-tissue pain are explained and discussed with different forms of suitable treatment.

The "slipped disk" in its various locations is explained and the treatment for mild and severe cases is outlined.

There are excellent chapters on both osteo-arthritis and rheumatoid arthritis, outlining the difference between the two conditions and explaining why the treatment is not the same for both. The importance of the role of exercises as the main part of physiotherapy in each condition is emphasized.

A chapter on the value and scope of appliances for the disabled rheumatic patient is a most useful feature.

Drs. Copeman and Mason are to be congratulated on the production of a really helpful book which can be recommended with certainty to rheumatic patients.

Oswald Savage.

Comment traiter la sciatique. By J. A. Lièvre. 1954. Éditions Médicales Flammarion, Paris.

This slim and comprehensive volume of just over 100 pages is based on a personal experience of 3,000 cases of sciatica. An historical survey is followed by a chapter on symptomatology and one on causation in which the discogenic theory is fully upheld. Chapters on treatment largely conform to current British practice, though with some divergences; firm beds, fracture-boards, and all forms of heat are condemned, but applications of cold are commended; epidural injections of procaine (lately supplanted by hydrocortisone) are more frequently used than in Great Britain and so is deep *x*-ray therapy. The last is used for the more chronic type of case and the series of treatments, applied to the lumbar region and affected limb, may total up to 2,000 r in males and post-menopausal females; in young women, however, irradiation is confined to the lower limb as the sympathy of French Courts of Law is apt to favour uninhibited ovarian function.

The book is provided with a list of 114 references and an index, yet, strangely, since it is so complete in many ways, it lacks a single diagram or *x*-ray photograph.

David Preiskel.

Atlas of Congenital Cardiac Disease. By Maude E. Abbott. 1954. American Heart Association, New York. ($5; 40*s.*)

The American Heart Association have performed a signal service to cardiology by making available once more this classic monograph in facsimile. The reproduction is most carefully done and of the highest standard.

The original 1936 edition is available in all important medical libraries, but the book has long been out of print: with the reawakening of interest in this field, many will be grateful to be able to obtain Maude Abbott's Atlas for their own shelves, since it is one that repays close and repeated study. E. G. L. Bywaters.

Ann. rheum. Dis. (1955), **14**, 93.

AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE FIRST INTERIM SCIENTIFIC SESSION

Dr. Edward Boland, President of the American Rheumatism Association, took the chair at the opening meeting of the first interim scientific session, held on November 4, 1954, at the Clinical Center, National Institutes of Health, Bethesda, Maryland.

Effect of Cortisone upon Regeneration. By HAROLD W. MANNER, *Utica, New York.*

Triturus viridescens viridescens, a urodele amphibian possessing the ability to regenerate limbs, was used in this study. After amputation, daily intramuscular injections of cortisone acetate were administered. Three groups were tested; one receiving 0·0005 mg., one 0·037 mg., and the control none.

In those animals receiving 0·0005 mg., a definite delay in wound healing was noted. Mitotic counts of epidermal and connective tissue cells revealed that cortisone inhibits wound healing by decreasing the rate of mitosis of both tissues. After 6 days, the animals adjusted to this dosage. A compensatory increase in the mitotic activity of epidermis and connective tissue followed. After 12 days, the experimental animals had completely overcome the initial inhibitory effect and regenerated at the same rate as the controls.

The most striking results were observed in those animals receiving 0·037 mg. daily. Gross morphological observations revealed a gradual degeneration of epidermis, dermis, muscle, connective tissue, and nerves in a proximal direction beginning at the amputation surface. This degeneration began on the 6th day and continued for a period of 14 days. The radius and ulna were the only elements left in the lower arm of some specimens. These bones were attached to the protruding humerus head by tendon remnants.

A complete histological study of these specimens is now being undertaken. This extensive degeneration appears to be due to an uncontrolled phagocytosis by those elements which usually leave the wound site after the inflammation reaction subsides.

Discussion.—DR. WILLIAM H. KAMMERER (*New York, N.Y.*): I am afraid I missed it if the Doctor stated the weight of the experimental animal. I wonder if he could correlate or compare the dosage of cortisone used in this experimental animal with that used in man.

DR. MANNER: We had that in mind when we set up the dosage of cortisone for these experimental animals, which was done on a weight proportion basis. The 0·0005 mg. is comparable to a 25-mg. dosage daily in a man weighing 120 lb.

DR. HANS WAINE (*Boston, Mass.*): I think it is particularly gratifying that Dr. Manner has again directed fundamental research to a group of animals with interesting articular structures. Lubosch (1910) called attention to the fact that certain of these amphibians throughout life, instead of the typical articulation that is found in the higher species, have synchondrotic joints. In other words, a rather primitive type of articular cartilage makes up the joint for the total adult life of the animal. For that reason, it appears that these animals would constitute a good model for studying the effects of various influences on differentiation of joint tissues in normal and abnormal conditions. Has Dr. Manner observed any effect on the articulations?

DR. MANNER: In a recently published report on the normal histology of regeneration we took that fact into account. In the adult animals the entire epiphyseal end of long bones is cartilaginous in nature. The fibroblasts which accumulate in the blastoma end—I use the term "fibroblasts" to denote an embryonal mesenchymal cell as distinct from a fibrocyte; some histology books use the term synonymously—are capable of differentiating into chondroblasts, which then become the chondrocytes of the adult cartilage. This is approximately the sequence that occurs in forming the new articular ends.

DR. CHARLES RAGAN (*New York, N.Y.*): What happens to regeneration in the salamanders when he "stresses" them, and is the whole process of regeneration dependent upon environmental temperature; do injections alone of an inoculant vehicle modify regeneration?

DR. MANNER: As to the effect of the environmental temperature upon regeneration, we find in most metabolic effects a direct correlation between rate and temperature; if the temperature is increased (and we tried it one summer where the running water in which these animals are kept reached a temperature of approximately 70°), the rate but not the quality of regeneration differs.

When we first started on the animals we injected the control animals as well as the experimental animals. The control animals were injected with a salamander isotonic salt solution, a mixture of various salts closely approaching the isotonic concentration of salts in the animal's tissue fluids. There appeared to be no effect upon the regeneration even though the animals were injected daily with this solution.

A "stress" situation arose where the animals were injected daily, as we used a size 18 needle and the tail is rather small.

Electrophoretic Analysis of Normal and Arthritic Synovial Fluid. By DAVID PLATT, WARD PIGMAN, K. LEMONE YIELDING, and HOWARD L. HOLLEY, *Birmingham, Ala.*

Electrophoretic analysis of normal synovial fluid has been carried out for the first time. The electrophoretic

patterns of normal synovial fluid differ significantly from those reported for traumatic and arthritic synovial fluid. An important difference was the presence in five of eight normal fluids of two components whose relative mobilities were faster than that of the albumin fraction. Previously, two rapid-moving components had been detected occasionally in the electrophoretic patterns reported for pathological fluids. To distinguish the second component from the previously known hyaluronic acid, it is proposed that it be known as the π component.

The relative mobilities of the components of normal synovial fluid differ from those of serum obtained from the same individuals and from arthritic fluid and serum. The relative mobilities of the arthritic fluids are similar to those reported by Perlmann, Ropes, Kaufman, and Bauer for traumatic fluid. The A/G ratio in the normal fluids was greater than that of the arthritic fluids.

Arthritic fluids from individuals at the acute and recovery stages were analysed and compared. Upon improvement of symptoms, the relative electrophoretic mobilities of the alpha-two and beta globulins increased. A decrease in the relative mobility of the hyaluronic acid also occurred upon clinical improvement. Other components showed a less marked effect. As might be expected, the relative mobilities approached those of the normal fluids as a result of the treatment. The electrophoretic analyses of synovial fluid were carried out using the Perkin-Elmer Model 38 Tiselius electrophoresis apparatus. The buffer used in this investigation was a veronal buffer, *p*H 8·6, ionic strength 0·1. The relative mobilities were determined by comparing the mobilities of the various components with that of the albumin fraction.

Discussion.—DR. MARIAN W. ROPES (*Boston, Mass.*): We have for years been hoping to find a component that moved with a mobility between that of hyaluronic acid and albumin. We have seen one such peak and one questionable peak in abnormal fluids. We hoped to find it because many of us think there may be, *in vivo*, a combination between hyaluronic acid and albumin, and we wonder whether this component will turn out to be such a combination.

In the matter of difference in mobilities in normal and abnormal fluids, we have been much disturbed; as Dr. Platt suggests, we should be interested in knowing whether the mobilities in normal fluid remain unchanged in fluid treated with hyaluronidase. We have found the mobilities in viscous fluids are not reliable, and that adding hyaluronidase to fluid or serum does not alter mobility or distribution of protein components; I think it is possible, therefore, that when hyaluronidase is added to normal fluid, the mobilities of normal fluids may approach those of all other fluids and of serum. We know that when we originally studied viscous fluid without hyaluronidase, we had variations in mobilities.

I think also it would be interesting to know the absolute mobilities rather than the relative ones, because of possible variations, although the results are so consistent that probably the relative mobilities are representative.

I find the so-called "π component" of extreme interest.

DR. PLATT: One of the difficulties in determining absolute mobilities in normal fluid components is the rather limited amount of the sample available for analysis. Generally we are quite fortunate if we obtain enough fluid for one sample. If conductivity measurements on the sample were carried out, there might not be a sufficient amount remaining for the electrophoretic run.

One other point. Perhaps we can also ascertain the mobilities by running them on the paper electrophoresis apparatus and checking them with the known absolute mobilities of some of the fluid we have analysed with the Tiselius apparatus.

DR. MORRIS ZIFF (*New York, N.Y.*): In 1940 Dr. Chargoff and I added heparin to plasma and observed little peaks migrating ahead of the albumin complex, very much like this π component, and I wonder whether this component is not a complex between albumin and hyaluronic acid.

DR. PLATT: It might be so. We do not know the chemical nature of these materials and are hoping to get some leads by use of the paper electrophoresis apparatus wherein we can use a fairly small sample for analysis.

DR. KARL MEYER (*New York, N.Y.*): I feel that this is an interaction of hyaluronic acid with one of the protein components. Dr. Ragan and I have investigated chemically quite a number of pathological synovial fluids and we never found any chemical difference between the latter and normal fluids, in our case only cattle synovial fluid. Cattle synovial fluid may not be quite normal, because of oedema in animals which have been transported.

What disturbs me more is the difference in mobility between the hyaluronic acids. Theoretically, of course, hyaluronic acid having only one carboxyl group per repeating unit should have the same mobility regardless of its degree of polymerization, if the viscosity is taken into consideration; I wonder whether that has been done, because in these highly viscous fluids, of course, the viscosity cannot be disregarded as it can in serum.

The formula used for calculating mobilities is of some significance here. There is, however, one possibility which occurs to me, and that is that in the normal fluid, parallel to the higher degree of polymerization of hyaluronic acid, the carboxyl groups are masked in contrast to the depolymerized fluids in which the carboxyl groups are unmasked and active. There is a possibility that that might explain this really enormous difference between the relative mobilities which Dr. Platt has shown here.

DR. PLATT: Since a high viscosity is a property of normal synovial fluid, to destroy or greatly decrease this property by artificial means, such as hyaluronidase, would then make the normal fluids resemble the arthritic fluids. The viscosity is lowered to some extent in the ascending cell of the electrophoresis apparatus, since the components move through the buffer. The possibility exists that the π component might be an instrumental anomaly, but since it appears in both the ascending and descending portions of the cell, the possibility of its being an anomaly seems remote.

Effect of Hydrocortisone on Radioactive Sulphur Uptake in Cartilage. By CHARLES W. DENKO, DELBERT M. BERGENSTAL, and ALLAN T. KENYON, *Chicago, Ill.*

Previous studies on the fixation of radioactive sulphur, S^{35}, into tissues have demonstrated its organic binding into connective tissue, especially cartilage. It is incorporated largely into sulphate-bearing compounds,

i.e. chondroitin sulphate. Growth hormone stimulates this process markedly in hypophysectomized rats.

The influence of hydrocortisone on sulphur uptake was investigated similarly, using young female rats. The synthetic activity of tissues in binding S^{35} was studied in varied states influenced by hydrocortisone, growth hormone, and combinations of hydrocortisone and growth hormone. Hormones were injected intraperitoneally daily for 4 days as was radio-sulphur. After the animals were killed tissues were removed, and ashed, sulphur precipitated as barium sulphate, and radioactivity determined as a measure of S^{35} fixation.

Hydrocortisone administration resulted in a decrease in concentration of S^{35} in the cartilage, xiphoid, costal, and articular tibial (as the tibial cap) of hypophysectomized rat. Growth also usually decreased. Growth hormone administration counteracted depressing influence of hydrocortisone; conversely, hydrocortisone inhibited growth-hormone in stimulating S^{35} fixation.

Discussion.—DR. THEODORE B. BAYLES (*Boston, Mass.*): Some years ago there emanated from the Rockefeller Institute a report on the effect of thyroid function on the incorporation of radioactive sulphur into the costal cartilage of growing rats, showing that if thiouracil was given to these animals there was a marked diminution in radioactive sulphur uptake, which could be reversed or corrected by the administration of thyroxin.

I do not wish to discuss whether cortisone depresses thyroid function or not, but I wondered if this factor was considered in these experiments.

DR. DENKO: We felt that the thyroid function might be important in the sulphur fixation of these animals. Therefore, we carefully did our first series of investigations on the effect of thyrotropin on these tissues. We found that thyrotropin had no stimulatory or inhibitory effect that we could note in our experimental procedure.

We also ran a few animals using thyroxin, and found that we could demonstrate no appreciable effect of thyroxin, either, so we felt that thyro, thyrotropin, and thyroxin had no appreciable influence in sulphur fixation in our experimental animals.

Therefore, we felt that whatever effect we got was directly due to hydrocortisone. Furthermore, the previous studies demonstrated that *in vitro* or tissue culture work showed that cortisone would inhibit the sulphur uptake and I feel somehow that the thyroid function would not enter into such a procedure.

Mucoprotein of Cartilage. By MAXWELL SCHUBERT, and JENNIE SHATTON, *New York, N.Y.*

From cartilage a material has been isolated which behaves as a single substance, a compound of chondroitin sulphate and protein, that is, a mucoprotein. It is soluble in water and gives viscous solutions. Precipitated from solution as different salts it shows a constant composition. It can be distinguished from mixtures of protein and chondroitin sulphate in three different ways. First, the protein of the mucoprotein cannot be precipitated by any of the usual protein precipitants. Second, the polysaccharide and protein are simultaneously adsorbed to kaolin and so the polysaccharide of the mucoprotein can be completely removed from solution by repeated treatment with kaolin. This is not true of free chondroitin sulphate. Third, the mucoprotein does not pass through a glass bacterial filter while free chondroitin sulphate passes through readily. The electrophoretic mobility of the mucoprotein appears to be identical with that of chondroitin sulphate. The mucoprotein in solution gives strongly metachromatic colours with appropriate dyes. The mucoprotein is susceptible to attack by two different enzymes, hyaluronidase and trypsin. Not more than half the chondroitin sulphate of cartilage could be extracted in the form of this mucoprotein. How the other half is bound is not yet clear. The existence of such a mucoprotein in connective tissue raises other possible interpretations of what is meant by depolymerization of ground substance, such as are thought to occur in rheumatic disease.

Relation of Mucoprotein, Mucopolysaccharides, and Collagen Formation. By THOMAS G. KANTOR, and MAXWELL SCHUBERT, *New York, N.Y.*

Chronic inflammations ending in dense scar formation are characteristic in the pathology of many arthritic conditions. Controlled foreign body reactions in subcutaneous tissue afford an opportunity to study the genesis of dense scar tissue histologically and chemically.

Quartz-induced granulomata were studied histologically in the subcutaneous tissue of rabbits and the time of reticulin and collagen formation determined. Histochemical tests were used to establish the presence of mucoproteins or mucopolysaccharides.

In addition, chemical studies of the same material have been performed at three stages during the development of these lesions. Collagenous tissue, hexosamine, and water content were all determined, and an attempt was made to isolate and characterize the polysaccharides.

Preliminary results indicate that non-hexosamine containing polysaccharides is present during the stage of reticulin formation. Hexosamine-containing polysaccharides are present at all stages, but particularly as the lesion matures and collagen is actively laid down.

Discussion.—DR. WARD PIGMAN (*University of Alabama*): We know that these mucopolysaccharides and mucoproteins may be quite soluble in water. It has been one of the difficulties in histological examinations of tissues that one must avoid extraction of such materials during the staining procedure. Dr. McManus and Dr. Mowry, at our school, have worked out a procedure which they applied particularly to protecting dextran in tissue, and this procedure involves using aqueous alcohol rather than aqueous pyruvic stain.

I wonder if you have gone into that at all here, because as you have already indicated, many of these materials are somewhat soluble. Has there been an attempt to avoid solubilitization during the staining procedure, with resultant loss of materials?

DR. KANTOR: My feeling is that the 10-minute procedure of periodate oxidation is probably not enough to get out too much in the way of soluble polysaccharides. We know from other staining methods (such as metachromicity and the Hale procedure) that it takes extensive washings at times to diminish the staining intensity of those other stains. It may be true, however, that the Schiff stain depends on a more soluble polysaccharide.

DR. PIGMAN: In your fixing procedure is there any possible loss of these materials at those times?

DR. KANTOR: The fixing procedure mainly is that of Carnoy, which is followed by strong alcohol dehydration. No water is used at all and we hope that Carnoy, which is a mucoprotein precipitant, will maintain the position of all the polysaccharides in the tissue.

DR. PIGMAN: These tissues contain water-soluble fractions, and generally most of these are not picked up in the usual procedures.

Further Studies on Mucopolysaccharides. By KARL MEYER, EUGENE A. DAVIDSON, ALFRED LINKER, and PHILIP HOFFMAN, *New York, N.Y.*

The mucopolysaccharides occur in mammalian connective tissues in complex patterns typical of the tissues of their origin. Since last year two new mucopolysaccharides have been isolated, keratosulphate and chondroitin. Keratosulphate is composed of equimolar concentrations of N-acetylglucosamine, galactose, and sulphate; its structure is still unknown. Chondroitin, composed of N-acetylgalactosamine and glucuronic acid, resembles hyaluronic acid in many of its physical and chemical properties. Both form highly viscous solutions and in both the hexosaminic bonds are hydrolysed by testicular and bacterial hyaluronidases at comparable rates. The bacterial hyaluronidases yield from both substrates 4-5 unsaturated hexuronides. The repeating deacetylated disaccharide of chondroitin was isolated in a yield of 75 per cent. and crystallized. Its infra red absorption spectrum was identical with that of the disaccharide chondrosin obtained from chondroitin sulphate A of cartilage and C of umbilical cord.

Studies of chondroitin sulphate B (which occurs in skin, heart valves, tendon and large blood vessels) revealed further differences from the other chondroitin sulphates. Besides its higher optical rotation and resistance to testicular hyaluronidase, it showed a markedly faster rate of acid hydrolysis than either A or C. One mole of CO_2 per repeating unit was liberated by decarboxylation, whereas the carbazole reaction for uronic acids gave only half the expected value. On acid hydrolysis, it yielded a disaccharide with infra red spectrum different from that of chondrosin. It thus shows little relation to the chondroitin sulphates, apart from its analytical values. The biological implications are being studied.

Agglutination and Inhibition by Serum Globulin in the Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis. By MORRIS ZIFF, PATRICIA BROWN, JACQUES BADIN, and CURRIER MCEWEN, *New York, N.Y.*

A naturally occurring inhibitor of the sensitized sheep cell agglutination reaction has been demonstrated in the globulin fraction of normal and pathological sera. Precipitation of the euglobulin fraction of rheumatoid serum effected partial removal of this inhibitor from the agglutinating factor, and increased the sensitivity of the agglutination reaction. The modified Rose test performed on the euglobulin fraction was compared with the modified Rose and Heller agglutination tests, using whole serum, and the modified Rose test on the cold globulin fraction in a group of patients with rheumatoid arthritis and in control individuals. The highest percentage of positive tests was obtained with the euglobulin fraction, and with a decrease in the percentage of false positive reactions.

The capacity of the euglobulin fraction of rheumatoid and non-rheumatoid sera to inhibit the agglutination of sensitized sheep cells by known positive test sera was also studied. It was found that non-rheumatoid euglobulin fractions inhibited the agglutination of sensitized cells by positive test sera, but that rheumatoid euglobulin did not. Specifically, 95 per cent. of non-rheumatoid euglobulin fractions thus far investigated inhibited agglutination in a significant titre, while rheumatoid euglobulin fractions failed to inhibit in all cases. This provides the basis for a sensitive test.

The difference in solubility of the agglutinating factor in rheumatoid arthritis and the false positive reaction of lupus erythematosus was observed.

Discussion.—DR. JOSEPH J. BUNIM (*Bethesda, Md*): Dr. Ziff and his associates are to be congratulated for an ingenious modification of the agglutination reaction which now enhances its diagnostic possibilities and usefulness. We have had the privilege of applying this modification during the past 3 months here at the Institute, and have found it most useful. There was a group of fourteen patients with rheumatoid arthritis who had a consistently negative sheep cell agglutination by the Heller technique. When retested by the modified technique of Ziff and his associates, eight of those fourteen were converted from negative to positive.

We also had one particularly impressive case of a little child with Still's disease, whom we were able to observe in the 6th week of her illness, and who had a definitely positive test by the euglobulin modification.

We have also found the test to be negative in spondylitis, and have been able to convert a positive reaction in a rheumatoid patient to a negative one by the intramuscular injection of human gamma globulin.

DR. WILLIAM KAMMERER (*New York, N.Y.*): When I first started work with Dr. Cecil some years ago, the "old" streptococcus agglutination test was in favour, and I learnt from him about its merits, demerits, and possible implications. I developed an interest in these biological phenomena, and was happy some 4 or 5 years ago when I was able to continue my interest in a small way in my association with Dr. George Heller at the Veterans Hospital, Bronx, N.Y., who has devoted himself to research in this field.

After Dr. Heller had made a modification of the original Rose test, which appeared to be an improvement, his chief interest focused on finding in what fraction of sera was the reactor responsible for this agglutination phenomenon. Naturally, his attention turned to the globulin fraction of serum and he demonstrated that the haemagglutination test for rheumatoid arthritis can be inhibited by including Plasma Fraction 2 as a reagent. Agglutination did occur with tannic acid erythrocytes sensitized with Fraction 2.

Nevertheless, the number of positive reactions with known cases of rheumatoid arthritis did not increase as he had hoped it would by using the tannic acid erythrocytes sensitized with Fraction 2 above the level that we obtained with whole serum, which was about 72 to 76 per cent.

He studied the other fractions of globulin that he had available and found that there was no inhibition with

Fraction I, IV-1, IV-4, and V, but, with Fraction III some degree of inhibition was obtained.

Regarding euglobulin, which is sort of a hodge-podge, which can be prepared by several different methods of salting, the interesting question is, what fraction of euglobulin is responsible for this phenomenon, particularly since the individual globulin fractions, as studied by Heller, did not enhance the sensitivity of the test.

I should like to know whether euglobulin prepared by other methods of salting have been used, and, if so, whether the results were any different?

Lastly, I should like to add my congratulations to those of Dr. Bunim, because I think that Dr. Ziff and his co-workers have furnished us with a diagnostic tool that may be very useful and helpful.

DR. ZIFF: I am not sure whether Heller, who has made excellent contributions in this field for many years, has actually tested directly with purified globulin fractions.

DR. KAMMERER: Yes, he has done it directly with purified globulin fractions as prepared by Cohn's cold ethanol method.

DR. ZIFF: Against tannic acid-treated cells, not against amboceptor-sensitized cells?

DR. KAMMERER: Against both.

DR. ZIFF: We have tested the euglobulin precipitate by the method of Dr. Nana Svartz of Sweden. We did not get as high a percentage of positives as she obtained in patients with rheumatoid arthritis, but no doubt this is because we are sensitizing differently and using different criteria for a positive test. I think the results depend upon the separation at least in part of the agglutinator from the inhibitor substance. No doubt we do not remove all the inhibitor, but sufficient appears to be removed, so that the percentage of positives goes up, and false positives down.

The test is somewhat more complicated. The dialysis procedure takes several days.

DR. RALPH H. BOOTS (*New York, N.Y.*): It seems to me that, despite the numerous agglutination tests which have been devised, the most useful diagnostic and laboratory procedure for differentiation of rheumatoid arthritis is still the determination of the sedimentation rate. As you will recall, this was first described in this country over 20 years ago by Dr. Dawson and myself; the method which we used was the Westergren modification of the Fahraeus technique. Since that time, there have been many modifications, and all of them seem to complicate the diagnostic procedure rather than to help it. It may be a different story with agglutination phenomena. Dr. Ziff's method of the sensitized sheep cell agglutination seems to be a distinct contribution and renders this type of test of more value.

The first agglutination phenomenon, the haemolytic streptococcus agglutination, was first introduced by Cecil, Nichols, and Stainsby to show the relationship between haemolytic streptococci and rheumatoid arthritis and not as a diagnostic procedure. It was only later that it was used for diagnosis.

Dr. Dawson and I found that its great disadvantage was that very few patients gave a positive test in the first year of the disease. Later, after 4 or 5 years, the percentage of positives would run as high as 80 per cent. In the late stages of the disease the diagnosis is so easy to make from clinical signs that the test, as we used it, was of relatively little value.

Dr. Ziff stated the number of positive agglutinations in relation to the duration of the disease; I should like to know whether he gets more positive agglutinations in patients with early rheumatoid arthritis than we obtained with the streptococcus agglutination test.

DR. ZIFF: The inhibition procedure is based on the ability of the euglobulin fraction to inhibit known positive serum. We have not found a patient with rheumatoid arthritis, even early, whose euglobulin fraction was able to inhibit a known positive serum. We assume that this means that there is sufficient agglutination in this fraction from rheumatoid serum to neutralize the inhibitor. It proves to be a more sensitive way of demonstrating the agglutination.

DR. CHARLES RAGAN (*New York, N.Y.*): Do your controls include any patients with rheumatic fever?

DR. ZIFF: There were fourteen with rheumatic fever.

DR. HOWARD C. COGGESHALL (*Washington, D.C.*): We found quite a number of patients with sensitive reactions to penicillin and sulpha and various serum had positive tests. I wonder if you have studied this aspect?

DR. ZIFF: The one case of serum sickness was negative.

DR. CURRIER MCEWEN: I have one comment on one of Dr. Boots's remarks. No one would want to deprecate the usefulness of the erythrocyte sedimentation rate or such a test as that for C-reactive protein, but they are non-specific tests and in no way selective, and do not distinguish between rheumatic fever, rheumatoid arthritis, lupus, etc. Therefore, it would be clinically very useful to have a test which is more selective for rheumatoid arthritis.

We do not believe that this modification of the sheep erythrocyte agglutination test has yet been brought to a point where it can be used with complete confidence diagnostically. When one is testing the diagnostic value of a new procedure, one uses it first on clinically clear-cut cases. We hope that it will prove useful in early cases not yet clinically diagnosable, but we do not want to be very emphatic about that yet. It will take much more observation and many more patients—especially earlier cases and those giving false positive results—before one can be sure of the reliability of the test.

DR. RUSSELL L. CECIL (*New York, N.Y.*): I think all these agglutination reactions have suffered from being a little too complicated for practical use in routine diagnosis. I wonder if Dr. Ziff could tell us just how practical his test would be for use in ordinary clinical laboratories. If it were not too complicated and there were not too many pitfalls, it would be a valuable addition to our diagnostic armamentarium.

DR. ZIFF: The inhibition test, I think, is difficult to do as a routine, because it is in a sense two tests. The direct test for agglutination, in which we found 92 per cent. positives, is more sensitive than the whole serum test and would be well worth doing. As it requires dialysis of serum for 2 days, it takes 2 days longer to get the answer.

Uricosuric Effect of Phenylbutazone. By E. R. HUFFMAN, C. J. SMYTH, GEORGE M. WILSON, JR. (by invitation), and ROBERT HILL (by invitation), *Denver, Colo.*

This investigation concerns the effect of oral phenylbutazone at various blood levels upon the serum and urinary uric acid in ten gouty and eight non-gouty arthritics. A step-wise fall in serum uric acid to normal occurred in all but two of the gouty patients. After a

lag of 2 to 3 days the serum uric acid fell an average of 3·5 mg. per cent. by the 8th day. The excretion of uric acid was increased in all but one patient and the maximum output occurred before the maximum fall in the serum level. The average daily increase in uric acid excretion in the gouty subjects was 325·1 mg.; in the non-gouty it was 151 mg. In the non-gouty subjects phenylbutazone produced an average fall in the serum uric acid level of 2·3 mg. per cent.

Renal clearance studies using simultaneous endogenous creatinine and uric acid showed that phenylbutazone above the serum levels of 10 mg. per cent. produced an increase in the C urate/C creatinine ratio in both gouty and non-gouty subjects. The magnitude of the fall in the serum uric acid correlated with the increase in the C urate/C creatinine ratio. It is concluded that phenylbutazone lowers the serum uric acid value largely by its uricosuric effect. Data from 73 patients who received oral phenylbutazone indicate that the majority who received 600 mg./24 hrs and all who received dosages higher than this had serum levels above 10 mg. per cent.

Discussion.—DR. OTTO STEINBROCKER (*New York, N.Y.*): I enjoyed hearing this careful and significant discussion of phenylbutazone excretion. We happen to have done a more limited study of the same subject, but we did not get the same results. Like several other observers, we were unable to demonstrate an increase of urate excretion during the administration of phenylbutazone. One of four patients showed a questionable increase of urate excretion and three showed none.

We think that the careful work just described must indicate that there is something about the technique of looking for these phenomena that evaded us. As many workers have found increased urate excretion with phenylbutazone as have found none.

Contradicting our own information, while we were doing these studies, two patients developed renal calculi; in one we were fortunate enough to get the calculus which proved to be pure urate.

We feel, from a clinical standpoint, that the paper just presented does reflect what happens, but that the mechanism is not quite clear. Very likely, during phenylbutazone therapy, urate is excreted in some complex not readily found by ordinary methods, and, for that reason, in several studies, including ours, the increased excretion was not demonstrated.

DR. WILSON: I think it is significant that the drug causes salt and water retention, and that with large doses it is difficult to demonstrate any uricosuria.

DR. JOHN NORRIE SWANSON (*Toronto, Ont., Canada*): I should like to support Dr. Wilson's contention that phenylbutazone is uricosuric. In two patients that we studied in our investigation unit on a standard diet, we, too, found that the output of uric acid in the urine was increased while taking this drug. Our study was very short, being only 4 days on each occasion, and I should like to ask whether Dr. Wilson found that this effect is maintained. In other words, is phenylbutazone an alternative to Benemid? Or is it better than Benemid or aspirin? Has he any data to show that if it is combined with either of these two drugs, its effect is complementary or antagonistic?

DR. WILSON: This is the most important aspect of the problem. In our experience, it requires 600 mg. phenylbutazone daily to attain a consistent blood level above 10 mg. per cent., the level at which significant uricosuria occurs. This is a rather large dose; in a small series of cases that we have analysed we were unable to maintain patients for a long period on this dosage without incurring toxic side-effects requiring discontinuance of the drug. We believe, therefore, that Benemid is the drug of choice for uricosuria therapy.

DR. JAMES WYNGAARDEN (*Bethesda, Md*): We have been interested in the effect of phenylbutazone on uric acid metabolism, since the early reports that it caused a decrease in serum urate concentration without a corresponding increase in urinary urate. We studied this problem in two normal subjects on a low purine, low protein diet. Analyses for uric acid were made by a specific enzymatic method (differential spectrophotometric method of Kalckar modified by Praetorius).

Tests were conducted with N^{15}-uric acid during control periods and again after several days of phenylbutazone 800 mg. per day. The variations of the miscible urate pool incident to drug ingestion were compared with rises in urinary urate excretion. The rates of turnover of urate were compared before and during drug ingestion. Catabolism and extrarenal disposal of urates were estimated from the fraction of the turnover failing to appear in urine, and also from the fraction of the test dose of N^{15}-uric acid failing to appear in urine. Finally, uric acid spaces were calculated for all experiments.

In both subjects the cumulative amounts of extra uric acid appearing in urine during drug ingestion agreed within 10 or 15 per cent. with the degrees of contraction of the miscible pool, so that it was apparent that the renal action of phenylbutazone explained the observed changes in serum urate levels.

There were no appreciable changes in the rates of uric acid synthesis. There were slight decreases in the amounts of uric acid catabolized or disposed of by non-renal pathways, and 20 to 35 per cent. increases in uric acid spaces between the control and later experiments, attributable I believe to fluid retention.

On the basis of these studies in two normal subjects, it would appear that phenylbutazone has only one important effect on uric acid metabolism—namely, the enhancement of urinary urate excretion.

DR. WILLIAM C. KUZELL (*San Francisco, Calif.*): Our results correspond more or less with those of Dr. Steinbrocker and his associates. We have been impressed by the fact that the anti-inflammatory effect of phenylbutazone does not depend on such large doses as are necessary to produce uricosuria. Furthermore, the use of quite small maintenance doses of phenylbutazone decreases the frequency of acute exacerbations without decreasing the serum uric acid. In studying patients for equally long periods before the administration of any drug, we frequently observed that they put out large amounts of urate in a cyclical fashion.

DR. WILSON: I agree that the uricosuric effect of this drug probably bears no relation to its remarkably dramatic effect in the acute gouty patient. We studied two patients during an acute attack of gout, who received 100 or 200 mg. of phenylbutazone every 2 hrs; we did repeat clearances at 4, 8, and 12 hrs, and were unable to demonstrate a significant blood level or any marked change in kidney function.

Uricolysis in the Normal and Gouty Human. By E. BIEN and M. ZUCKER, *Long Island, N.Y.*

The lack of uricase in humans has been used as evidence that uric acid is not degraded. Wyngaarden and Stetten

demonstrated that the nitrogen of uric acid labelled with N^{15}, when injected into a normal human is in part excreted in the urinary urea and ammonia. Marked alteration in the intestinal flora by sulphonamide therapy did not diminish the extent of degradation. Additional evidence for uricolysis is the uric acid "deficit" observed by Benedict and her co-workers in their studies on the uric acid turn-over and pool. Tuttle and Cohen demonstrated oxidation or uric acid by a peroxidase, and Margoles and Griffiths found similar results with a cytochrome—cytochrome oxidase system.

Whole blood contains both of the above enzyme systems. The rate of uricolysis in whole blood was determined. Since leucocytes contain large amounts of peroxidase, and erythrocytes have both peroxidative and cytochrome activity, *the formed elements were separated and incubated with plasma.* Addition of urate, such that the plasma of normal individuals was at hyperuricaemic levels, did not change the rate of uricolysis. Repeat determinations at weekly intervals showed only minor variations. The rate of uricolysis was determined in hospitalized individuals without hyperuricaemia or joint symptoms. In the normal individuals, there was no difference in the rate of uricolysis between males and females. Eight determinations on seven gouty individuals showed that the addition of colchicine had no effect on the rate of uricolysis. A diminished rate of uricolysis was observed in whole blood and with both white and red cells in patients with gout. There was no correlation between the degree of hyperuricaemia and the rate of uricolysis. The results were as follows:

Subjects	Number of Determinations	Per cent. Plasma	Mean Fall (per cent.) in Plasma Urate Incubated with		
			Whole Blood	White Blood Cells	Red Blood Cells
Normal ..	25	2·3	34·4	39·0	29·8
Gouty ..	8	3·5	23·2	26·5	19·2

Discussion.—DR. L. MAXWELL LOCKIE (*Buffalo, N.Y.*): Was freezing used in any of these studies?

DR. BIEN: There was no freezing. The blood specimens were obtained and the experiment was started usually within an hour.

Comparative Pathology of Experimental Arthritis due to Formalin, Blood, Immediate and Delayed-Type Hypersensitivity Reactions. By D. BOCKING and F. S. BRIEN, *London, Ontario, Canada.*

In these experiments, the intra-articular lesions of immediate-type (anaphylactic) and delayed-type (bacterial) hypersensitivity in rabbits were compared. The immediate-type reaction was studied using egg albumen in rabbits actively sensitized. The delayed-type reactions were produced with old tuberculin (O.T.) injected intra-articularly in B.C.G.-sensitized rabbits. In addition, lesions produced by intra-articular injection of homologous blood and formalin were studied. In each group, the injections ranged from one to ten at 48-hr intervals.

The immediate-type hypersensitivity reaction resulting from a single injection of egg albumen consisted mainly of a polymorphonuclear exudate, maximal at 6 hrs. The delayed-type hypersensitivity reaction, with a single injection of O.T., consisted primarily of a synoviocytic and subintimal fixed-cell proliferation, with lymphocytic and polymorphonuclear infiltration, and superficial "fibrinoid" deposition—maximal at 48 hrs or later. Repeated intra-articular injections of egg albumen or O.T. in normal and sensitized rabbits produced a proliferative synovitis characterized by fibrinous exudate and infiltrate on the surface, synoviocytic and subintimal fixed-cell proliferation, and lymphocytic infiltration. In addition to these changes, repeated intra-articular injections of O.T. in sensitized rabbits caused an early pannus formation, subchondral bone invasion, and lymphoid collections.

Lesions resulting from formalin were characterized by extensive necrosis of cartilage, and subsequently, synovial membrane and adjacent bone, with relatively slight inflammatory reaction. It did not resemble the proliferative synovitis of rheumatoid arthritis.

Repeated intra-articular injections of homologous blood resulted in a mild proliferative synovitis.

Delayed-type hypersensitivity reactions simulated the histological appearances of rheumatoid arthritis.

Sternoclavicular Articulation in Rheumatic Diseases. By LEON SOKOLOFF and I. O. GLEASON, *Bethesda, Md.*

The sternoclavicular articulation is affected by various types of rheumatic disorder with greater frequency than is recognized clinically. This is illustrated by several examples of rheumatoid arthritis, gout, and infectious synovitis. The normal joint and the degenerative changes occurring with age were shown to distinguish them from the specific lesions of rheumatoid arthritis. Examination of this structure is recommended when other polyarthritic joints are dissected at necropsy.

Review of the Published Data on a Syndrome resembling Rheumatoid Arthritis, Disseminated Lupus, and possibly other Collagen Diseases, induced by Hydralazine and other Hypotensive Agents. By JOHN LANSBURY and FRED B. ROGERS, *Philadelphia, Pa.*

The occurrence during hydralazine administration of syndromes closely resembling those of rheumatoid arthritis and disseminated lupus erythematosus is an event of major importance. It seems that for the first time we have been able to induce a clinical picture closely resembling two or more connective-tissue diseases. Thus the mechanism of production of the same symptoms in spontaneous rheumatic disease may be discovered.

These artificially produced syndromes are not identical with the spontaneously occurring diseases. The drug-induced syndrome may not apply to both rheumatoid arthritis and disseminated lupus, but may represent gradations of lupoid disease alone. The high incidence (7·5 per cent.) of the drug-induced syndrome makes it unlikely that we are seeing here simply the precipitation of a latent rheumatoid or lupoid stage. We cannot dismiss these findings with a statement that they are

simply a "drug reaction". The important thing is that parallel mechanisms seem to be involved in both the drug-induced and spontaneously occurring syndromes.

Allergy, disturbed liver function, and blockade of the nervous pathways and blood-pressure-regulating mechanism may play a part in this process.

The pulmonary fibrosis occurring in hexamethonium administration, which histologically resembles scleroderma of the lungs, may also have some relevance.

Discussion.—DR. VIRGINIA P. BEELAR (*Washington, D.C.*): I reported a case in November, 1953, in which symptoms very typical of rheumatoid arthritis developed in a patient receiving doses of less than 100 mg. per day. Subsequently her sister also developed a similar syndrome on approximately 200 mg. a day. I do not feel therefore that excessive dosage is entirely the explanation.

DR. LANSBURY: I am very glad to have this information One other patient in whom the syndrome did occur on rather small dosage turned out to have lupus when the records were examined.

DR. BEELAR: I followed this patient carefully during the last year, and her sedimentation rate has continued elevated without apparent explanation. She has had no further rheumatic symptoms of any sort.

DR. HILARY H. HOLMES (*New York, N.Y.*): Is there any chemical method for determining hydralazine in the urine or blood.

DR. LANSBURY: Hydralazine can be determined in the urine, but it is most unlikely that any substance resembling hydralazine will be found to occur naturally in the body.

DR. CHARLES L. SHORT (*Boston, Mass.*): This is an important subject, in that it represents the first experimental production of a syndrome resembling rheumatoid arthritis or disseminated lupus.

I should like to confirm the apparent antagonism between severe hypertension and rheumatoid arthritis. We are not yet sure that rheumatoids are apt to show hypotension or to have, in a large series, lower blood pressures than controls. But thus far, in a series numbering 600-800 rheumatoid patients, we have not encountered any who have died from severe hypertension at an early age. We have found this situation in two patients with rheumatoid spondylitis, but not in any with peripheral rheumatoid arthritis. I think this suggests that there is an antagonism between the two conditions.

I should also like to ask whether the rauwolfia compounds have produced any symptoms of a syndrome resembling this one. Just before I left Boston I had been seeing a spondylitic who had a moderate hypertension. He was being treated with rauwolfia and just when his diastolic pressure came down to a satisfactory level, a severe iritis developed.

DR. LANSBURY: I don't know whether it is in the literature, but it is quite common knowledge that the administration of rauwolfia and its preparations to hypertensives may be associated with muscle pains. Whether this has any meaning in the rheumatological sense or not I don't know, but it is an interesting point.

DR. WILLIAM C. KUZELL (*San Francisco, Calif.*): We approached this problem in a somewhat different way: in studying the ratio of the reduced to the oxidized glutathione in the blood of a great many subjects with a variety of rheumatic diseases, we found that the group comprising the most severe rheumatoid patients had the lowest ratios. The total blood glutathione was normal, but reduced glutathione in the blood was decreased.

These rheumatoid people were generally also hypotensive. When they were treated in various ways and improved clinically the glutathione ratio rose. In trying to correlate the rise in the glutathione ratio with all other measurements, the only one which paralleled the rise in the glutathione ratio was the rise in the blood pressure.

The therapeutic agents which seemed to cause this change most regularly were cortisone and corticotropin.

Use of Combined Therapy and Rebound Suppression in the Treatment of Rheumatic Fever. By EDWARD E. FISCHEL and CHARLES W. FRANK, *New York, N.Y.*

In most instances of rheumatic fever, salicylate and adrenocortical hormones appear to be equally effective in suppressing signs of activity. In severe cases, the combined use of both agents may offer some advantage, perhaps of a synergistic nature, in effecting rapid defervescence of inflammation. Toxicity of the hormones may be partially avoided by early withdrawal. The severity of the anticipated rebound can be substantially diminished by continued administration of salicylate.

Day-to-day changes in the severity of rheumatic carditis are difficult to evaluate. The presence of other systemic or local signs of rheumatic activity reflects the possibility of an associated rheumatic carditis. Studies of the clinical evidences of rheumatic activity in conjunction with determinations of the E.S.R., serum complement, and C-reactive protein were done to aid the detection of inflammatory reaction.

In general it appears advisable to institute therapy which effects early, rapid, and prolonged suppression of rheumatic inflammation. Drug toxicity and the hazards of discontinuing therapy should be minimal.

Discussion.—DR. CURRIER MCEWEN (*New York, N.Y.*): Dr. Fischel has done us all a service in recalling attention to the possible usefulness of salicylates in the treatment of rheumatic fever beyond the antisymptomatic and antipyretic effect.

Probably no one has been more insistent than I in the past that salicylates are useless so far as any benefit in carditis is concerned. The evidence to-day does not prove that the impression which most of us have had for many years is wrong. Dr. Fischel has been a lone voice in the wilderness for a number of years, and, largely through his work, we now have some reason to believe that the salicylates may have some beneficial effect in carditis. Certainly, the evidence is now overwhelming that the salicylate effect is not mediated through the adrenocortical mechanism, and if that is the case, it seems to me there is justification for using salicylates as well as cortisone or ACTH in rheumatic carditis.

It is difficult to judge, to-day, whether any of these agents plays any very pronounced role in controlling carditis; but in the present unfortunate state of uncertainty, I believe it is reasonable to suggest that a patient with carditis deserves the benefit of both hormone and aspirin therapy if one wants to do the best one can on the basis of the meagre information available.

Enzymatic Metabolism of Corticosteroids. By KURT J. ISSELBACHER and GORDON TOMKINS, *Bethesda, Md.* (Introduced by Joseph J. Bunim.)

The major pathway of adrenal steroid inactivation

results in the formation of the corresponding tetrahydro derivatives. This involves the addition of four hydrogens to the ketone and double bond of ring A. These reactions occur primarily in the liver, as previously demonstrated by perfusion and slice experiments. However, in such preparations, where cellular structure is maintained, it is not possible to make a detailed study of the enzymes and coenzymes involved.

By means of extracts free of intact cells, we have demonstrated that an enzyme system capable of converting cortisone to tetrahydrocortisone resides in the granule-free cytoplasm of the rat liver. The cofactors for these reactions are the reduced forms of the di- and tripho-sphopyridine nucleotides. In addition, it has been observed that the enzyme involved in the reduction of cortisone is different from that concerned in the inactivation of hydrocortisone. These enzymes have been separated.

Preliminary Clinical Trials with 9-Alpha-Fluoro Hydrocortisone Acetate in Rheumatoid Arthritis. By EDWARD W. BOLAND and NATHAN E. HEADLEY, *Los Angeles, Calif.*

A halogenated derivative of hydrocortisone—9-alpha-fluoro hydrocortisone acetate—was administered as investigative therapy to thirteen patients with active rheumatoid arthritis. Seven patients received the preparation as initial medication; three of these were transferred later to hydrocortisone (free alcohol) for comparisons of dosage requirements. Six patients, being maintained on established daily amounts of hydrocortisone (free alcohol), were transferred directly to the fluoro compound and comparisons of the doses needed for similar degrees of rheumatic control were made.

The following conclusions were drawn:

(1) Weight for weight, the antirheumatic potency of 9-alpha-fluoro hydrocortisone acetate was found to be much greater than that of the parent compound, hydrocortisone. This was indicated by the following:

(*a*) Initial suppressive doses of the fluoro derivative ranging from 3 to 8 mg. a day were sufficient, in five of seven patients, to promote rapid improvement in the rheumatic manifestations.

(*b*) Comparisons of maintenance dosage requirements for approximately equivalent degrees of clinical control revealed that, in eight of nine patients, the antirheumatic power of 9-alpha-fluoro hydrocortisone acetate, milligram for milligram, was roughly ten times that of hydrocortisone (free alcohol).

(2) With the small total daily amounts of the fluoro compound employed, signs of fluid retention developed in twelve of the thirteen patients, being pronounced in some. This suggested that the substitution of a fluorine atom at the ninth carbon position increased the electrolyte activity of hydrocortisone to an extent proportionately greater than it enhanced its antiphlogistic property. The excessive salt-and-water retaining effect of the fluoro derivative would seem to preclude its practical application in systemic therapy.

(3) The observations with 9-alpha-fluoro hydrocortisone acetate are of interest chiefly because they demonstrate that the anti-inflammatory potency of hydrocortisone may be enhanced, and other of its properties modified, by altering its formula. This raises hope that, through changes in structure or other chemical substitutions, a more successful therapeutic agent for rheumatoid arthritis may be produced in the future.

Effects of Aldosterone and 9-Alpha-Fluoro Hydrocortisone Acetate administered to Rheumatoid Patients: Preliminary Report. By L. EMMERSON WARD, HOWARD F. POLLEY, CHARLES H. SLOCUMB, and PHILIP S. HENCH, *Rochester, Minn.*

Aldosterone was administered intramuscularly for 6 days to two patients who had rheumatoid arthritis. Total daily doses were 200, 250, 400, 800, and 280 μg. in one patient; 800, 800, 800, 600, 1,000, and 640 μg. in the second. No antirheumatic effect could be detected clinically after the use of these doses in these patients. Retention of fluid and sodium chloride occurred. Detailed studies, including studies of metabolic balance, were made in one patient. The doses used in this preliminary study were considerably larger than those reported to be effective in studies on patients with Addison's disease. However, the range of doses necessary for production of antirheumatic effects, if any, may not have been reached by the doses used in this study. When supplies of aldosterone permit, larger doses will be employed for further study of antirheumatic, anti-inflammatory, and other effects. The compound, 9-alpha-fluoro hydrocortisone acetate, administered orally to a group of rheumatoid patients in total doses of 4 to 8 mg. daily produced cortisone-like antirheumatic effects. These same doses also produced potent metabolic activities, particularly in regard to retention of sodium chloride and fluid, and excretion of potassium.

Discussion.—DR. CLARK (*Denver, Colo.*): We have treated nine patients who had previously been regulated on cortisone dosage varying from 50 to 67 mg. per day with doses of 9-alpha-fluoro hydrocortisone acetate ranging between 3 and 4 mg. per day. All except one of our patients developed signs of toxicity which necessitated discontinuing the drug. Eight gained weight up to 10 lb. and seven of them developed moderate to severe oedema. Five developed hypertension. One showed a systolic blood pressure rising to 210 and developed albuminuria; neither symptom disappeared until 2 weeks after discontinuing the drug.

Three patients spontaneously reported a distressingly severe nasty taste in the mouth, with scum forming on the teeth, and were very belligerent about taking the drug.

In four patients who developed insomnia and five who had severe headaches the drug was discontinued.

The one patient who showed no large weight gain and no toxic symptoms received potassium supplements in his diet, 0·6 g. three times a day; he has been on the drug since the middle of July and is still taking it with no apparent ill effects. He was taking 67 mg. cortisone daily and is now well regulated on 3 mg. 9-alpha-fluoro hydrocortisone acetate.

We did balance studies on two of our patients, and, as far as their sodium and potassium were concerned, both showed a marked fall in sodium excretion on a controlled intake of sodium and potassium, the excretion

fell from 120 to 130 milli-equivalents per day to 6 milli-equivalents per day in one, and 9 in the other.

Our observations are almost exactly the same as Dr. Boland has reported, and agree with Dr. Ward's finding regarding the electrolyte balance.

DR. THEODORE B. BAYLES (*Boston, Mass.*): I do not feel that 9-alpha-fluoro hydrocortisone, or perhaps any other type of cortisone, is the answer to rheumatoid arthritis, but in our experience, running as long as 30 days on individual patients, we saw very little evidence of hypertension or weight gain.

We studied five hospitalized patients on low sodium diets of 1 g. or less and were receiving 0·6 g. potassium chloride three times daily. The dosage ranged from 4-16 mg. daily for 10 days. The 9-alpha-fluoro hydrocortisone was given orally every 6 hours. This does not mean that I feel this rigid programme is desirable, but it does seem that with this programme one can carry patients for a fairly long time with a fairly good dosage.

I agree that its antiphlogistic effect is about seven times that of hydrocortisone.

DR. BOLAND: I did not wish to infer that it is impossible to continue 9-alpha-fluoro hydrocortisone acetate administration in some patients. We have treated three patients for uninterrupted periods of 4 to 5 months, but two showed moderate rises in blood pressure and one showed varying degrees of oedema. All the patients in the reported series, save one, were treated on an ambulatory basis, and adhered to qualitative, not quantitative, restriction of sodium in their diets.

Considering the frequency of unwanted side-reactions, particularly fluid retention and blood pressure elevation, no patient in the reported series was better controlled with 9-alpha-fluoro hydrocortisone acetate than with hydrocortisone (free alcohol), even though much larger doses of the latter were required. For this reason 9-alpha-fluoro hydrocortisone acetate is decidedly inferior to hydrocortisone as a therapeutic agent and in our opinion it would not be practical for general use.

We have also administered 9-alpha-fluoro hydrocortisone (free alcohol) orally, and the results in patients with rheumatoid arthritis are roughly the same as with the acetate ester.

The importance of these findings with 9-alpha-fluoro hydrocortisone is the demonstration that the anti-inflammatory property of hydrocortisone may be enhanced by a change in its formula. It was obvious from various studies, including our own investigations (which compared the effects of cortisone, hydrocortisone, and their several esters) that some of the physiological actions of hydrocortisone could be modified through alterations in its chemical structure. It was surprising to us, however, that the anti-inflammatory activity could actually be made greater than that of the natural hormone. This observation is significant because it implies that through further alterations in the steroid nucleus, a compound may be contrived which possesses wide dissociation between wanted anti-inflammatory action and certain other physiological effects which we now look upon as unwanted endocrine or metabolic complications.

DR. JOSEPH L. HOLLANDER (*Philadelphia, Pa*): Our group has had an opportunity to study 9-alpha-fluoro hydrocortisone acetate injected intra-articularly in 35 cases of rheumatoid arthritis. We noted a local anti-rheumatic effect clinically from as little as 3 mg. by intra-articular injection, but in most cases 5 mg. was necessary. The effect of this dose in no case exceeded that of 37·5 mg. hydrocortisone acetate in anti-inflammatory potency or in duration of effect.

Frequently, when the dose was increased to 7·5 mg. into one knee, or 5 mg. into each knee, marked oedema of the leg or legs developed and persisted for several days. This is probably our most interesting observation, that we could produce local oedema in the leg injected, without giving systemic cortisone.

Our findings thus confirm the markedly increased potency of this analogue, but the increased salt-retention effect appears to nullify this advantage so far as intra-articular injection is concerned.

DR. JOHN W. SIGLER (*Detroit, Mich.*): We have used 9-alpha-fluoro hydrocortisone intra-articularly in two patients. In one of these, recurrent peptic ulcer pain was noted after a 5-mg. injection into the knee joint.

Preliminary Observations on the Antirheumatic Potency, Metabolic Effects, and Hormonal Properties of Metacortandralone and Metacortandracin. By JOSEPH J. BUNIM, MAURICE M. PECHET, and ALFRED J. BOLLET, *Bethesda, Md.*

Metacortandralone is a crystalline synthetic steroid possessing the physiological activity of an adrenocortical hormone. A decrease of more than 50 per cent. in the circulating eosinophils and a reduction in the urinary 17-ketosteroids occurs 1 or 2 days after its oral administration.

Metacortandralone is an effective antirheumatic agent. Each of the indices of objective joint changes (swelling, tenderness, warmth, pain on motion, and range of motion) was significantly, rapidly, and consistently improved. Subjective improvement, both articular and general, was striking and was greater than objective improvement. Metacortandralone is an anti-inflammatory agent. Histological examination of synovial biopsies taken before and during its administration clearly demonstrated a marked subsidence of inflammation. The erythrocyte sedimentation rate and C-reactive protein were restored to normal (or near normal) in every case studied. The sensitized sheep cell reaction of the serum was not significantly altered.

Metacortandralone is approximately three to four times more potent than cortisone and two to three times more potent than hydrocortisone. Preliminary observations indicate that this enhanced potency is not accompanied by a proportionate increase in the frequency or severity of undesirable side-effects. This new steroid therefore possesses an augmented therapeutic ratio. The maintenance dose varies with the severity of the arthritis and has ranged from 5 to 25 mg. daily.

Haemopoietic stimulation resulted from the administration of metacortandralone. In several patients significant increases occurred in the haematocrit, haemoglobin, red and white blood cells, and neutrophils.

The total cholesterol but not the cholesterol-ester increased as the steroid was administered.

Balance studies on two patients with rheumatoid arthritis—one male aged 16 and one female aged 32—demonstrated that the daily oral administration of 30 mg. metacortandralone for twelve successive days caused no sodium retention and no loss of potassium or nitrogen. When the daily dose was increased from

30 to 50 mg. (in the male patient) for 24 successive days, a negative nitrogen balance, consisting of a loss of 1·8 g. nitrogen daily, developed on and after the tenth day. The serum albumin fraction increased by an average of 0·7 g. per cent., and the serum globulin fraction decreased by an average of 0·9 g. per cent. The fasting blood sugar revealed no significant increase during metacortandralone administration. No patient developed glycosuria.

The undesirable effects thus far observed have been minor in nature and degree and often disappeared as the dose was decreased. These consisted of hirsutism, faint facial rounding, acne-form eruption, increased perspiration, increased appetite, transitory epigastric discomfort, fatigue, weakness, sleeplessness, and transitory mental depression, but not hypertension.

When the steroid was discontinued or the dose reduced below the minimal level, signs and symptoms of arthritis returned within a few days.

Metacortandracin, a member of the same family of synthetic crystalline steroids, appears to possess hormonal properties, antirheumatic effectiveness and potency, and a therapeutic ratio like those of metacortandralone.

This is a preliminary report based on short-term observation of only seven cases of rheumatoid arthritis, and we do not yet know what effects, favourable or unfavourable, will result from prolonged administration.

CHAIRMAN KAMMERER: I think it would certainly be no exaggeration to say that Dr. Bunim's work may well be the most exciting therapeutic event that we have heard of since May of 1950. His work is so new that it probably isn't appropriate to ask for discussion, but we will entertain any questions that may come from the floor.

DR. CHARLES RAGAN (*New York, N.Y.*): We are becoming aware of the changes in effects which may be brought about by minor changes in the chemical structure of these various steroids. Can Dr. Bunim tell us anything about the structure of metacortandracin?

DR. BUNIM: I do not know the chemical structure of this steroid, and I am told by the manufacturers (Schering) that they do not yet know it either.

DR. RAGAN: How was it found to be anti-inflammatory? Was it found in screening a bunch of steroids on a laboratory shelf?

DR. BUNIM: The research team of Schering Corporation have done a number of experiments on animals, and have found that these steroids possess the capacity to reduce the eosinophil count and to cause thymic involution. It was, therefore, their interest or curiosity which led them to inquire whether this substance might not also possess anti-inflammatory, anti-rheumatic capacities, and we were very glad to try to determine that for them by tests with human subjects.

DR. CHARLEY J. SMYTH (*Denver, Colo.*): I think we have witnessed a paper not unlike that of Hench, Kendall, Slocumb, and Polley in May, 1949; the date August 3, 1954, may also become an epoch in medical history. But since 1949, those of us who are interested in rheumatoid arthritis have been particularly concerned about the long-term results. Dr. Bunim has stressed, I think very properly, the fact that these are short-term studies. We have now followed in our clinic four patients for over 3½ years. We have seen patients with relatively early rheumatoid arthritis maintained continuously, and have seen the progression of rheumatoid arthritis manifested by involvement of additional joints, development of subcutaneous nodules, and progressive joint destruction. It is to be emphasized that these changes have occurred in spite of intensive, carefully controlled long-term hormone administration.

Our current feeling (and I am sure it is shared by many in this room) is that so far hormonal therapy in rheumatoid arthritis has not altered the ultimate progress of the pathological process of the disease, although the patients may have symptomatic relief and be much more comfortable, and able to lead a more productive life.

We should keep the long-term view in mind, because rheumatoid arthritis is often extremely protracted.

DR. BUNIM: At the Heart Institute in this Clinical Center, the effects of this drug on nephrosis was studied in two patients, and one of them developed a complication which I think ought to be discussed. A 29-year-old male had had nephrosis for 9 years and was becoming progressively worse. In January, 1954, he was treated with cortisone and then with hydrocortisone. Unusually large doses were used and he was receiving 300 mg. daily.

When no favourable effect, or only slight improvement, was observed, the drug was discontinued after having been administered for 4 months. There was a hiatus of 3 months, in which he received no steroids. He was then put on metacortandralone, first in doses of 40 mg. a day for a period of 16 days and then of 70 mg., which is higher than the dosage we have used. He remained on this dosage for 10 days, and it was tapered during the next 4 days, and finally discontinued.

Five days after the last dose was given, the patient passed a tarry stool. He continued to bleed from the gastro-intestinal tract; finally he was operated upon and an ulcer was found in the posterior wall of the stomach, close to the pyloric sphincter. In the floor of this ulcer was a branch of the gastro-epiploic artery. A gastric resection was done and the patient recovered.

How much the antecedent steroid therapy of cortisone and hydrocortisone and the metacortandralone contributed to this ulcer, we do not know. The patient had no symptoms, and an *x* ray of the stomach and duodenum was negative 2 weeks before the tarry stool was noted.

PAPERS PRESENTED BY TITLE ONLY

Hormonal Control of Amino Acid Metabolism. By VICTOR H. AUERBACH, *Boston, Mass.*

Effect of Salt on the Biophysical Characteristics of Sodium Hyaluronate. By BARUCH BLUMBERG and KARL MEYER, *New York, N.Y.*

Clinical Experience with Phenylbutazone. By CHARLES W. DENKO, DAVID RUML, and DELBERT M. BERGENSTAL, *Chicago, Ill.*

Chemical Fractionation of a Type-6 Strain of Group-A Haemolytic Streptococcus. By J. WILFRED HAHN and BETTY HARGIS, *Chicago, Ill.*

Adenosine Mono- and Di-nucleotide in the Pathogenesis of Rheumatoid Arthritis. By GREGORY HAYDU, *New York, N.Y.*

Flocculation Tests in Rheumatoid Arthritis. By JACQUES HOULI, *Rio de Janeiro, Brazil.*

Human Skin Collagen from Different Age Groups before and after Collagenase Digestion. An Electron Microscopic Study.* By MADELINE K. KEECH, *New Haven, Conn.*

* See this issue, p. 19.

Psychic and Physical Findings in the Fibromyalgias. By J. H. IRVINE, *New York, N.Y.*

Serum Protein-Polysaccharide as an Aid in the Evaluation of Rheumatoid Arthritis. By W. K. ISHMAEL, M. R. SHETLAR, A. A. HELLBAUM, and R. W. PAYNE, *Oklahoma City, Okla.*

Observations on the Effects of Intra-Articular Phenylbutazone. By DAVID H. NEUSTADT, *Louisville, Ky*, and OTTO STEINBROCKER, *New York, N.Y.*

Clinical Efficacy of Corticotrophin—Zinc Hydroxide in Patients with Rheumatoid Arthritis. By HAROLD S. RUBIN and HEINRICH G. BRUGSH, *Boston, Mass.*

Observations on Phenylbutazone Therapy in Acute Rheumatic Fever with Heart Involvement. By ARTHUR L. SCHERBEL and FENTON SCHAFFNER, *Great Lakes, Ill.*

Rheumatoid Heart Disease associated with Rheumatoid Spondylitis. By CHARLES LEROY STEINBERG, *Rochester, N.Y.*

FUTURE ARRANGEMENTS

The annual general meeting, 1955, will be held on June 3 and 4, at Atlantic City, immediately before the meeting of the American Medical Association.*

In 1957 the annual meeting will be supplanted by the IX International Congress of the Ligue Internationale contre le Rhumatisme, which will take place on June 23-28 at Toronto, Canada.

It has been decided to replace the *Annual Directory of the American Rheumatism Association* for 1955 by the forthcoming new edition of the *Year-Book of the Ligue Internationale* (Secretary: Dr. Richard T. Smith). This is the official directory of the international organization and will include the names and addresses of members and officers, and particulars of the committees, etc., of the American Rheumatism Association, as well as those of all other affiliated rheumatological societies.

An American Journal of Rheumatology.—A committee of the A.R.A. to explore the desirability and feasibility of establishing a new journal of rheumatology, with Dr. Joseph Hollander as Chairman, was set up by approval of the Executive Committee in 1953. This Committee reported to the Executive Committee in June, 1954, and the latter decided that the time was not yet ripe for such an undertaking, that further study and consideration would be forthcoming, and that a subsequent report should be made to the members concerning this proposed journal. Dr. Hollander's committee prepared such a report on the pros and cons of the matter with the co-operation of Dr. Philip Hench. At the Executive Committee meeting in November, 1954, it was decided to poll the membership to obtain their reaction to the creation of such a journal.

* Applications for reservations to: Dr. Clarence Whims, Ventnor Clinic, 5407 Atlantic Avenue, Atlantic City, N.J.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

The Third European Rheumatology Congress will be held in Scheveningen, The Hague, from June 13-17, 1955. To enable definite arrangements to be made, those intending to attend the Congress are particularly requested to apply for membership and hotel accommodation as soon as possible.

Secretary-General:

Burg. de Monchyplein 9, The Hague.
Telephone: 185281, ext. 1267.
Telegraphic address: Rheumacongres.

The Congress fees should be paid through the intermediary of a Bank to the Amsterdamsche Bank N.V., The Hague, in favour of the Treasurer of the Third European Rheumatology Congress, before May 1, 1955. After this date the fees will be raised.

Scientific Programme

Section 1. Rheumatic Fever

Dr. E. G. L. BYWATERS (*England*): The U.S.-U.K. co-operative rheumatic fever trial.

Prof. Dr. F. COSTE (*France*): Le traitement de la maladie de Bouillaud.

Dr. P. VAN DER MEER (*Netherlands*): Frequency of rheumatic heart disease in school children and its consequences, a study of the Rotterdam primary school population.

Dr. GENE H. STOLLERMAN (*U.S.A.*): Prophylaxis of rheumatic fever.

Section 2. Connective Tissue

Drs L. E. GLYNN, R. CONSDEN, J. HOLBOROW, E. G. L. BYWATERS (*England*): Abnormalities in rheumatic diseases with special reference to polysaccharides and proteins.

Dr. G. ASBOE-HANSEN (*Denmark*): Hormonal control of connective tissue.

Prof. Dr. G. C. HERINGA (*Netherlands*): Mucopolysaccharides in connective tissues.

Dr. MORRIS ZIFF (*U.S.A.*): Studies on the alteration of connective tissue in the collagen diseases.

Section 3. Osteo-Arthritis of the Spine and Disk Degeneration

Prof. Dr. STEN FRIBERG (*Sweden*): Lumbar disk degeneration in the problem of low back and sciatic pain.

Prof. Dr. S. DE SÈZE and Dr. J. LACAPÈRE (*France*): Spondylose déformante et dégénération du disque intervertébral: L'aspect clinique, radiologique, et expérimental du problème.

Dr. P. BARCELO and Dr. J. M. VILASECA SABATER (*Spain*): The interapo-physeal joints of the spine.

Prof. Dr. H. JUNGHANNS (*Germany*): Spondylose und degenerative Bandscheibenveränderungen.

Section 4. Rheumatism and Social Medicine

Dr. R. J. WEISSENBACH and Dr. F. FRANÇON (*France*): Répartition et incidences sociales suivant les différents types de rhumatismes.

Prof. Dr. K. M. WALTHARD (*Switzerland*): Rhumatisme et la médecine sociale en Suisse.

Prof. Dr. A. MASTURZO (*Italy*): Les aspects professionnels du problème social du rhumatisme.

Prof. Dr. E. W. BAADER (*Germany*): Die soziale Bedeutung des Rheumatismus in Deutschland.

Dr. M. RUELLE and Dr. A. HENRAARD (*Belgium*): Le problème social de la polyarthrite chronique évolutive.

HEBERDEN SOCIETY

At a **Clinical Meeting** held at the Royal Free Hospital, London, on February 18, 1955, the following papers were presented:

Dr. J. H. JACOBS: Viscosity Studies on Hyaluronic Acid of Synovial Fluid.

Dr. CLIFFORD ROSE: Masked Pneumonia occurring during Cortisone Therapy.

Mr. CHARLES GRAY: Flexor Tenosynovitis round the Wrist Joint.

Mr. R. MARKHAM: Paper Electrophoresis of Serum Mucoproteins.

Dr. A. ST. J. DIXON: Dye Retention in Rheumatoid Arthritis: Relationship to Methods of measuring Blood Volume in this Disease.*

Dr. A. T. RICHARDSON demonstrated a case of Shoulder-hand syndrome, Dr. E. HESS a case of Lupus disseminatus erythematosus.

Demonstrations were set up to show: the measurement of synovial fluid viscosity, the electrophoretic pattern of blood mucoproteins, and the measurement of joint temperature.

* This issue, p. 51.

FIRST CANADIAN CONFERENCE ON RESEARCH IN THE RHEUMATIC DISEASES, 1955

A conference on research in the rheumatic diseases sponsored by the Canadian Arthritis and Rheumatism Society, was held at Sunnybrook Veterans Hospital, Toronto, on March 4, 1955. The following papers were given:

Chemical Composition of Connective Tissue, R. H. Pearce and H. G. Vance (*London, Ont.*).

Factors involved in Histamine-Induced Arthritis and Rheumatism in Animals, S. H. Bensley (*Toronto*).

Morphological Evidence of the Hypersensitive Pathogenesis of Collagen Disease and its Experimental Counterpart, H. Movat and R. N. More (*Kingston, Ont.*).

Recent Studies on Anaphylactoid Inflammation, G. Jasmin and H. Selye (*Montreal*).

Corticosteroids of Normal and Arthritic Human Blood before and after Administration of Corticotrophin, M. Darrach (*Vancouver, B.C.*).

Steroid Hormones and Arthritis, A. G. Gornall (*Toronto*).

Studies in the Plasma Proteins in Rheumatoid Arthritis, J. A. Dauphinée and A. Bruce-Robertson (*Toronto*).

Treatment of Rheumatic Fever, J. D. Keith (*Toronto*).

Pathogenesis, Interpretation, and Specificity of the L.E. Cell Reaction, M. A. Ogryzlo (*Toronto*).

Experimental and Clinical Data on a Nicotine Acid Cream as a Diagnostic Aid in Rheumatoid Arthritis, De G. Vaillancourt (*Montreal*).

Metabolic Aspects of Rheumatoid Arthritis, L. G. Johnston and K. R. Mackenzie (*Montreal*).

Long-term Use of ACTH and Adrenal Steroids in the Rheumatic Diseases, N. Swanson (*Toronto*).

FIRST PAN-AMERICAN CONGRESS ON RHEUMATIC DISEASE, 1955

The First Pan-American Congress on Rheumatic Disease will be held under the auspices of the Pan-American League against Rheumatism on August 14 to 20, 1955, in Rio de Janeiro and Saõ Paulo, Brazil. The Brazilian Rheumatism Society will act as host. All interested physicians and scientists are cordially welcomed to participate in this Congress. Scientific reports should be offered to the Secretary of the Brazilian Rheumatism Society, from whom further information may be obtained:

Dr. Waldemar Bianchi, *Secretary*,
126 Avenida Franklin D. Roosevelt,
Rio de Janeiro, Brazil.

It is hoped that in the future congresses will be held at intervals of 4 years, mid-way between the International Congresses on Rheumatic Diseases, and in parallel with the European Congresses on Rheumatic Diseases.

SOCIETÀ ITALIANA DI REUMATOLOGIA

THIRD ROME RHEUMATOLOGY DAY, 1955

At a meeting organized by the Centro di Reumatologia di Roma on February 12 and 13, 1955, the chair was taken by Prof. Antonio Gasbarrini.

The opening papers were presented by Prof. S. de Sèze (*Paris*) on "Structural deterioration of the intervertebral disks", and Prof. A. Robecchi (*Turin*) on "The shoulder-hand syndrome".

DUBLIN RHEUMATISM ASSOCIATION

The Annual Report for 1952-53 of this Association can be obtained by application to the Director at 34 Upper Mount Street, Dublin. In addition to a number of Tables analysing the work of the treatment clinic during this period, interesting accounts are included of the VIII International Congress of Rheumatic Diseases, held in Geneva, which was attended by Dr. O'Reilly, and of the arthritis programme of the National Institute of Arthritis and Metabolic Diseases in Washington. The brief survey of the rheumatism problem in Ireland clearly shows the need for yet further investigation of the various medical and sociological factors involved. The Association are to be congratulated on the steady development of their pioneer work.

W.S.C.C.

Ann. rheum. Dis. (1955), **14**, 107.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Heart Failure in Children with Active Rheumatic Carditis. THOMAS, G. (1954). *Brit. med. J.*, **2**, 205. 3 figs, 7 refs.

In this paper from the Canadian Red Cross Memorial Hospital, Taplow, Bucks, it is suggested that in rheumatic carditis in children, abnormal signs attributed to heart failure, which is less common than was formerly supposed, are in reality often due to pericardial effusion. Though the distinction may sometimes be difficult, it is well defined in the series of thirty cases here described.

Of these thirty cases, 23 in which pericardial effusion was diagnosed were all febrile at the onset—as often occurs early in a first attack. Common features included tachypnoea, chest pain, raised jugular venous pressure, abnormal signs at the lung bases, especially on the left side (usually due to pleural effusion), and leucocytosis. A high erythrocyte sedimentation rate and rapid changes in the heart size and shape as observed radiologically were invariable. The condition was not found to respond to digitalis. Although four of these 23 patients died, the prognosis is considered to be better than in cases of heart failure.

The other seven patients, who had heart failure, were all afebrile. Failure occurred only in the presence of well-marked valvular lesions and cardiac enlargement, late in the disease or in second attacks. In all cases there were raised venous pressure and hepatic enlargement; five had râles at the lung bases, but none had pleural effusion; peripheral oedema and ascites both occurred in two cases. Increased body weight was observed only in the presence of peripheral oedema. There was no leucocytosis, but in all cases there was a low or sharply falling erythrocyte sedimentation rate. The heart size increased slightly in three, but no rapid changes in size and shape were seen. Four cases responded well to digitalis, supplemented if necessary by low-sodium diet and mercurial diuretics; in the other three an initial response was succeeded by increased signs of failure and death in 2 to 6 weeks.

Details of two of the cases are presented to illustrate the differential features between the two conditions.

R. S. Stevens.

Evaluation of Large Doses of Cortisone in First Attacks of Rheumatic Carditis. HEFFER, E. T., TURIN, R. D., SLATER, S. R., and KROOP, I. G. (1954). *J. Pediat.*, **44**, 630. 17 refs.

The authors claim that early and intensive treatment with cortisone in doses adjusted to the individual case may prevent residual cardiac damage in first attacks of rheumatic carditis. In support of this claim they report the results in nineteen cases in children aged between 5 and 15 years of age treated at the Jewish Hospital, Brooklyn, New York, all of whom were suffering from a first attack of rheumatic fever with carditis. The initial daily dose of cortisone was between 200 and 300 mg., divided in four oral doses. This was given for 2 weeks or longer until the disease process appeared to be suppressed, when the dose was reduced; the usual duration of treatment was 5 or 6 weeks. All the cases were carefully observed and blood counts and laboratory tests for rheumatic activity were carried out.

The authors were unable to find any residual cardiac damage in thirteen of the children during an observation period varying from 6 to 14 months; all these thirteen cases had been treated within the first 2 weeks of the illness. The remaining six patients, who were all treated later in the disease, had a systolic murmur at the end of the period of observation. Most of the patients showed a rebound phenomenon when the drug was stopped.

[The authors' conclusion that "our experience also indicates that cortisone in adequate dosage may be more effective in controlling carditis than salicylates" is hardly warranted, for there were no controls. The results achieved in this series appear to be very good, but they do not correspond with those achieved by others who have used the same treatment. The value of cortisone in the treatment of rheumatic fever can only be assessed by properly controlled studies.] *R. S. Illingworth.*

Rheumatic Fever Prophylaxis. Control of Streptococcal Upper Respiratory Infection in Cardiac and Rheumatic Fever Patients and their Siblings; Preliminary Report. TIDWELL, R. A. (1954). *Northw. med.* (*Seattle*), **53**, 470. 24 refs.

It is pointed out that long-continued administration

of penicillin as a prophylactic against streptococcal infection of the upper respiratory tract is considered essential in the management of patients with cardiac disease or a history of rheumatic fever. All subjects with active infection are possible future victims of rheumatic fever, and since carriers of the streptococcus may endanger the health of contacts, family prophylaxis has been recommended.

At the out-patient clinic of the Children's Orthopaedic Hospital, Seattle, a single daily dose of a slowly-excreted penicillin, "bicillin" (dibenzylethylendiamine dipenicillin G), was given by mouth to 57 children and two adults for periods ranging from 3 to 10 months. Of the 59 patients, 25 were ill at the beginning of the treatment, and among the remainder were eight with congenital heart disease and thirteen with a history of rheumatic fever. All the patients were given one tablet (containing 200,000 units of bicillin) daily. In spite of a fairly constant exposure to infection, throat cultures examined monthly remained consistently negative for β-haemolytic streptococcus, except in two cases. There was no recurrence of rheumatic fever in the affected patients and no evidence of bacterial endocarditis in those with congenital or rheumatic heart disease. Time lost from school was reduced by over 80 per cent. compared with the time lost by the same group in the year preceding the start of prophylactic treatment. The author concludes that a single daily dose of bicillin is effective in eliminating the haemolytic streptococcus from the pharynx, and preventing a recurrence of rheumatic fever.

[No results are reported for a similar group not receiving penicillin prophylaxis. The efficacy of the drug in preventing recurrences of rheumatic fever is scarcely proven by these observations.] *Kenneth Stone.*

Relation of the Serum Inhibitor of Serum-extracted Streptolysin-S to Serum Phospholipid from the Standpoint of Rheumatic Fever. WALLIS, A. D., and VIERGIVER, E. (1954). *Amer. J. med. Sci.*, **227**, 431. 1 fig., 13 refs.

There is a growing conviction that the haemolytic streptococcus is the cause of rheumatic fever, presumably acting through some antigen–antibody mechanism. An investigation was carried out at Pennsylvania Hospital, Philadelphia, to determine whether streptolysin-S is the streptococcal component responsible for rheumatic fever. Serum from healthy subjects and from hospital patients, both children and adults (illness not specified), was analysed for its phospholipid content and for the inhibitor of streptolysin-S, the method of Youngburg and Youngburg being used for estimation of phospholipid. Streptolysin-S inhibitor was measured, normal human erythrocytes being used, against serum-extracted haemolysin contained in the supernatant of broth serum cultures of a strain of streptococcus which produced streptolysin-S but no streptolysin-O. This supernatant, being unstable, was preserved at −16° C. or lyophilized, remaining potent at a titre up to 1 : 320 or 1 : 640 for at least 2 years. A haemolysin titration against a dilution of standard human serum and erythrocytes was made as a preliminary to each test in order to determine the combining dilution of haemolysin for each particular batch of erythrocytes.

The results showed that there was no real change with postprandial increase in serum phospholipid content; a low serum phospholipid level was found in association with a very weak streptolysin-S inhibitor, but with medium and high phospholipid levels the correlation was less definite.

Since it has been shown that the serum phospholipid level tends to be below normal in individuals who are susceptible to rheumatic fever, the authors consider that their findings lend support to the view that streptolysin-S may be the cause of this disease, and that susceptibility to it may vary inversely with the strength of the natural serum inhibitor of streptolysin-S. *E. G. L. Bywaters.*

Failure to Produce Rheumatic Fever in Rabbits by Prolonged and Intensive Streptococcus Infection. ROBINSON, J. J. (1954). *Arch. Path.* (*Chicago*), **57**, 516. 9 refs.

To determine whether rheumatic lesions might be the result of prolonged and severe streptococcal infection, 15- to 18-hour brain–heart-infusion neopeptone broth cultures of streptococci and staphylococci were injected intracutaneously and later subcutaneously, intramuscularly, and intravenously into groups of rabbits about twice a week for average periods ranging from 85 to 204 days. The seventeen groups each containing five to 27 rabbits, the total being 280, and the organisms injected included four types of Group-A streptococci (Types 10, 12, 14, and 19), one Group-C streptococcus, and two types of alpha-haemolytic streptococci, alone and in combination with Group-A types, as well as *Staphylococcus aureus* and *Staph. albus*. One group served as controls. The animals were examined daily and weighed twice weekly, and occasionally blood was taken for antistreptolysin-O titration, culture, or cell count. The animals were killed at intervals from 6 months onwards, and necropsy was performed and sections of various organs examined without knowledge of the organism received by the animal under examination.

Weight loss and signs of chronic disease were seen in those groups injected with *Staph. aureus* and Group-A haemolytic streptococci. Arthritis of a septic type, nephritis, and septic carditis were common, but no true Aschoff bodies were encountered. Carditis was found only in two rabbits suffering from the naturally occurring disease which is often termed *Encephalitozoon cuniculi* infection, one of which had received Group-A streptococci of Type 12 and the other an alpha-haemolytic streptococcus. The fibrinoid degeneration, myocardial injury, and chronic inflammation seen in these rabbits resembled those of rheumatic fever, but again no Aschoff bodies were seen. Infection with two types of organism produced changes no different from those produced by a single one.

The question of synergistic action among infective agents in the pathogenesis of rheumatic fever is suggested as a suitable subject for research. *E. G. L. Bywaters.*

Intramuscular Benzathine Penicillin in the Prophylaxis of Streptococcal Infection in Rheumatic Children. PERRY, C. B., and GILLESPIE, W. A. (1954). *Brit. med. J.*, **2**, 729. 6 refs.

The object of the investigation described in this paper from the United Bristol Hospitals (University of Bristol) was to determine the value of benzathine penicillin (N,N′-dibenzylethylenediamine penicillin G) in the prophylaxis of streptococcal infection in patients who had had rheumatic fever. To 22 rheumatic children, fifteen of whom had been persistent carriers of Group-A haemolytic streptococci for 4 to 9 weeks, the antibiotic was given intramuscularly at monthly intervals in doses of 1·5 mega units each; one child received five doses, seven received four doses, six received three doses, five received two doses, and three received only one dose. The serum penicillin level was estimated 4, 11, 18, and 25 days after the injection. Most of the injections caused local tenderness for 24 to 48 hrs, and in eighteen out of 67 instances slight fever was noted on the day after injection. On the 4th day the serum concentration of the drug ranged from 0·24 to 0·025 unit per ml. (average 0·08); on the 11th it ranged from 0·14 to 0 unit per ml. (average 0·043); on the 18th day from 0·1 to 0 unit per ml. (average 0·029); and on the 25th day from 0·07 to 0 unit per ml. (average 0·012).

Within 4 days Group-A streptococci were eliminated from the throats of all except one of the fifteen persistent carriers. New infections were almost, though not completely, prevented. *R. S. Illingworth.*

Skin Test with Streptolysin-O. (Test cutaneo alla O-streptolisina.) CORBELLI, G., and BRUNELLI, M. A. (1954). *Minerva med.* (*Torino*), **2**, 871. 5 figs, 17 refs.

At the University Medical Clinic, Bologna, skin tests were performed with a commercial product, used for the estimation of serum antistreptolysin, which contains a known amount of streptolysin-O and small amounts of other streptococcal products. In this method the amount of streptolysin is expressed in terms of a "combining unit", which is defined as the maximum quantity of toxin which, in the presence of a unit of antistreptolysin, does not produce haemolysis of 0·5 ml. rabbit erythrocytes in 5 per cent. isotonic solution. A quantity ranging from 0·1 to 0·15 ml. of a solution of this lyophilized, standardized, and sterilized streptolysin containing one combining unit in 1,000 or 2,000 ml. was injected into the flexor surface of the forearm. [No control injections were apparently given, except as stated below.] The reaction was regarded as positive when there was a fairly intense, clearly demarcated oedema and erythema, reaching its maximum after 20 to 30 hrs and then gradually but completely disappearing. Results were read at 24 hrs; reactions less than 10 mm. in diameter were ignored, and larger positive reactions were graded according to degree. The test was performed on 152 "normal" subjects (that is, patients considered free from streptococcal infection), 136 patients with upper respiratory infections, and 108 with rheumatic disease. In addition, 94 "normal" subjects were similarly tested with a suspension of a 24-hr culture containing 5,000,000 haemolytic streptococci per ml.

In the normal subjects the proportion of positive reactions to streptolysin-O averaged 9·8 per cent., and to the streptococcal suspension 30·8 per cent. In patients with acute infections of the upper respiratory tract positive reactions to streptolysin occurred in 52·9 per cent., and in those with chronic infections in 92·1 per cent. No constant correlation with organisms found in the throat was established, and no definitive explanation of the findings is offered. Of 23 patients with articular rheumatism also tested, 22 gave positive results, while of 85 patients with rheumatic cardiac lesions but no articular lesions a positive result was obtained in 56 cases. The occurrence of positive reactions coincided with clinical and pathological indications of activity. The authors suggest that cardiac lesions only become evident when activity is diminishing, and hence positive results of this test are accordingly less frequent.

W. A. Bourne.

Comparative Effects of Aspirin, ACTH, and Cortisone on the Antistreptolysin-O Titre and Gamma Globulin Concentration in Rheumatic Fever. STOLZER, B. L., HOUSER, H. B., and CLARK, E. J. (1954). *J. Lab. clin. Med.*, **44**, 229. 2 figs, 9 refs.

The comparative effects of aspirin, ACTH, and cortisone on the serum antistreptolysin-O titre and γ globulin concentration in rheumatic fever was studied at a U.S. Air Force Base Hospital in Wyoming. A total of 144 young adult males were divided by random selection into three groups, receiving respectively aspirin, ACTH. and cortisone. The drugs were given in a diminishing dosage for 6 weeks in all except eight cases, these requiring a further 4 weeks' treatment because of continued rheumatic activity. An intramuscular injection of 600,000 units of penicillin was given on the day of admission and then every 3 days for four injections; thereafter each patient received 1 g. sulphadiazine by mouth daily.

The antistreptolysin-O titre and the γ globulin concentration were estimated weekly in half the patients and at 10-day intervals in the remainder. The average values week by week for each of the three treatment groups are plotted on graphs. These show that both values fell most rapidly in the group receiving ACTH and least rapidly in the group receiving aspirin. It is stated (though the evidence is not given) that at the end of treatment the values were significantly lower in the ACTH group than in either of the other two groups, and that the difference between the values in the cortisone-treated group and those in the group receiving aspirin was not statistically significant. After treatment ceased there was a slight increase in the average γ globulin concentration in all three groups, coincident with a slight "rebound", which was noted clinically in some cases. Thereafter, there was a continued fall, and 14 months after the start of treatment the average γ globulin concentration was the same in both the ACTH- and cortisone-treated groups, the concentration in the aspirin-treated group being slightly higher.

The authors suggest that the difference between the

effect of ACTH and that of cortisone may have been related to the dosage of each drug, the patients receiving cortisone showing fewer signs of hyperadrenalism.

B. E. W. Mace.

Results of Hormone Therapy in Acute Rheumatic Carditis. (Résultants du traitement hormonal de la maladie de Bouillaud.) MOZZICONACCI, P., NOUAILLE, J., ATTAL, C., and CARAMANIAN, M. K. (1954). *Bull. Soc. med. Hop. Paris*, **70**, 786.

The authors give an interim report on the treatment with steroid hormones of 267 cases of rheumatic fever associated with carditis, some of which have been observed for more than 2 years. The results have varied; in most cases, however, the treatment was rapidly successful in reducing the activity of recurrent attacks, and this has led them to adopt steroid therapy as the basal treatment for this disease. They consider that it should be employed early in all cases of acute rheumatism, whether accompanied by carditis or not. They also give salicylates, and regard the use of antibiotics in addition as helpful in certain cases, as tending to prevent the occurrence of bacterial endocarditis on the site of an old valvular lesion. *W. S. C. Copeman.*

Rheumatic Heart Disease in Pregnancy. MACLEOD, M (1954). *Lancet*, **2**, 668. 20 refs.

It is pointed out that the effect of pregnancy on patients with mitral stenosis is to accentuate the natural features of the disease. The risk to life arises from acute pulmonary oedema and, to a lesser extent, from congestive heart failure. Early recognition of pulmonary hypertension and the efficient treatment of acute pulmonary oedema will contribute to a reduction in maternal mortality.

The author, writing from Aberdeen University, discusses his findings in one hundred cases of rheumatic heart disease in pregnancy, in 83 of which there was mitral disease and in seventeen mitral disease with aortic incompetence. Symptoms were classed as mild in 28 cases, moderate in sixty, and severe in twelve. Pregnancy was terminated in six of the patients with moderately severe symptoms and in six with severe symptoms. In the series as a whole there were three neonatal deaths and one stillbirth, but no maternal deaths. None of the patients was subjected to valvotomy. [This paper is of value because it indicates the results to be expected in these cases with expert obstetrical management in the absence of cardiac surgery.] *T. Semple.*

Study of Minute-to-Minute Changes of Arteriovenous Oxygen Content Difference, Oxygen Uptake, and Cardiac Output, and Rate of Achievement of a Steady State during Exercise in Rheumatic Heart Disease. DONALD, K. W., BISHOP, J. M., and WADE, O. L. (1954). *J. clin. Invest.*, **33**, 1146. 9 figs, 8 refs.

The authors, from the Queen Elizabeth Hospital, Birmingham, describe a technique for measuring changes in venous and arterial blood oxygen saturation, and thus in cardiac output, during 5 minutes' exercise and subsequent recovery in patients with rheumatic heart disease. The errors of the method, which are discussed, were found not to be of significant importance. In over half of the cases studied a steady state—that is, no important change or trend—in oxygen uptake, arterio-venous oxygen difference, or cardiac output was observed after 2 or 3 minutes; in severe cases in which the cardiac output was not raised on exercise and there was an abnormally high arterio-venous oxygen difference a longer time was required to reach equilibrium. There appeared to be no correlation between the degree of dyspnoea and the ventilation, the level of mixed venous oxygen saturation, cardiac output, pulmonary arterial pressure, or pulmonary capillary pressure.

J. Shillingford.

Prevention of Systemic Arterial Embolism in Chronic Rheumatic Heart Disease by means of Protracted Anticoagulant Therapy. WOOD, J. C., and CONN, H. L. (1954). *Circulation (N.Y.)*, **10**, 517. 29 refs.

Rheumatic Mitral Valve Disease over the Age of 50. [In English.] HEBBERT, F. J., and RANKIN, J. (1954). *Acta med. scand.*, **150**, 101. 40 refs.

Treatment and After-Care of Acute Rheumatism. (Traitement et surveillance du rhumatisme articulaire aigu.) CARAMANIAN, M. (1954). *Rev. Rhum.*, **21**, 664. 37 refs.

Rheumatic Fever and Active Rheumatic Heart Disease. ROBERTS, E. (1954). *Med. Clin. N. Amer.*, **38**, 1705. 25 refs.

Prevention of Rheumatic Fever. (Möjligheten av profylax mot reumatisk feber.) EDSTRÖM, G. (1954). *Nord. Med.*, **52**, 1366. 1 fig., 25 refs.

Aetiologic Factors in Rheumatic Fever. HARRIS, T. N. (1954). *Med. Clin. N. Amer.*, **38**, 1693. 41 refs.

Rheumatic Fever: Aetiologic and Prophylactic Considerations. The Association between Haemolytic Streptococci and Rheumatic Fever. (Febris rheumatica ur etiologisk och profylaktisk synpunkt. Sambandet mellan hämolytiska streptokokker och reumatisk feber.) WINBLAD, S. (1954). *Nord. Med.*, **52**, 1360. 10 refs.

Hypersensitivity and Rheumatic Fever. AIKAWA, J. K. (1954). *Ann. intern. Med.*, **41**, 576. Bibliography.

Chronic Progressive Inflammatory Rheumatism in Infancy. (Considérations sur les rhumatismes chroniques progressifs inflammatoires de l'enfance.) FRANÇON, F. (1954). *Rev. argent. Reum.*, **19**, 106.

Cortisone in Small Doses, Salicylates, and Antibiotics in Rheumatic Fever. (Cortisone a piccole dosi, salicilici ed antibiotici nel R.A.A.) POLI, M., DESTEFANIS, E., and CONTERNO, G. (1954). *Minerva med. (Torino)*, **2**, 1229. 1 fig., bibl.

Side-Effects, Complications, and Results of Hormone Treatment in Rheumatic Fever with Carditis. (Incidents, accidents et résultats du traitement hormonal de la maladie de Bouillaud.) D'OELSNITZ, M., GIOANNI, T., and DESESTRES, —. (1954). *Pediatrie*, **9**, 705. 27 refs.

Treatment of Rheumatic Fever with Large Doses of Cortisone. KROOP, I. G. (1954). *N.Y. St. J. Med.*, **54**, 2699. 27 refs.

Necessity of Adequate Steroid Dosage in the Treatment of Rheumatic Myocarditis. GRUBB, K. P., and HINES, J. J. (1954). *Quart. Bull. Northw. Univ. med. Sch.*, **28**, 260. 1 fig., 5 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Effects of Nitrogen Mustard Therapy in Patients with Rheumatoid Arthritis. PAUL, W. D., HODGES, R. E., BEAN, W. B., ROUTH, J. I., and DAUM, K. (1954). *Arch. phys. Med.*, **35**, 371. 7 figs, 22 refs.

Nitrogen mustard has been shown to inhibit a number of hypersensitivity phenomena; it suppresses local tissue reactivity, inhibits antibody formation, and blocks antigen–antibody combinations. These findings suggested to the authors the use of nitrogen mustard in the treatment of rheumatoid arthritis.

At the hospital of the State University of Iowa College of Medicine, seventeen patients with severe, active, deforming rheumatoid arthritis of long duration were studied for 8 months. The study was divided into four periods of 2 months each, 2 weeks of each period being spent in hospital and the remaining 6 weeks at home. During each period in hospital an extensive laboratory investigation was conducted in a metabolic ward, and the patient's clinical condition and particularly range of joint movement were assessed. For the first 4 months of the trial (that is, the first two periods) the patients were treated only by physical therapy and aspirin, but during the third period in hospital, nitrogen mustard was given in a dose of 0·1 mg./kg. body weight daily for 4 days. To reduce the incidence of vomiting, pentobarbitone and pethidine were administered beforehand. In the majority of patients, subjective improvement in joint pain began after the second dose of nitrogen mustard. In two cases in which the arthritis was accompanied by marked oedema of the lower extremities and severe joint effusion, treatment with nitrogen mustard resulted in a prompt diuresis, followed by disappearance of the oedema and marked reduction of the effusions. All but one of the patients showed an increase in joint mobility after treatment, in spite of the fact that the improvement due to the previous forms of treatment had reached its maximum after 4 months. The subsequent improvement in joint mobility was fairly well maintained for 12 weeks.

Laboratory studies carried out after the administration of nitrogen mustard showed the following results. There was a slight decrease in the erythrocyte count and haemoglobin level, and the leucocyte count decreased, reaching its lowest level about one week after completion of treatment, and then slowly returned to normal; the erythrocyte sedimentation rate was unchanged. The urinary excretion of 17-ketosteroids, and their ratio to creatinine, were normal and were not changed by treatment. The number of eosinophil leucocytes remained unchanged despite the temporary leucopenia, so that a relative eosinophilia existed for a few days. The glucose tolerance curves had shown a slight impairment of carbohydrate utilization and this was unchanged after treatment. The "bromsulphalein" test of liver function and the protein-bound iodine content of the plasma were normal before and after therapy. Electrophoretic analysis of the plasma proteins revealed abnormalities characteristic of rheumatoid arthritis, but after treatment with nitrogen mustard the various fractions tended to shift towards the normal. During and after treatment there was marked improvement in calcium balance. During therapy, heavy losses of nitrogen and phosphorus occurred, but this was due in part to decreased intake, and was followed by a gradual return to pre-treatment levels. The changes in the eosinophil and erythrocyte counts, sedimentation rate, 17-ketosteroid excretion, glucose tolerance, and calcium excretion, and the absence of hirsutism, elevation of the blood pressure, oedema, acne, or "moonface", suggest that the action of nitrogen mustard is not similar to that of cortisone and ACTH.

A. Swan.

Low Diastolic Pressure as a Clinical Feature of Rheumatoid Arthritis and its Possible Aetiologic Significance. TURNER, L. W., and LANSBURY, J. (1954). *Amer. J. med. Sci.*, **227**, 503. 1 fig., 9 refs.

The blood pressure readings of 320 patients with rheumatoid arthritis of at least 9 months' duration, admitted to Temple University Hospital, Philadelphia, were compared with the values in the published results for a series of 5,540 presumably normal subjects; in the case of the patients the pressure was determined on admission to hospital, in order to discount the hypotensive effect of subsequent bed rest.

The results showed that the average blood pressure (by decades) in the arthritic group was significantly lower than in the control group, ranging from 115/74 to 127/75 mm. Hg in the former, and from 120/77 to 166/92 mm. Hg in the latter. The average diastolic pressure of the arthritic patients remained virtually unchanged through all age decades from 20 to 70 years at about 75 mm. Hg, whereas that in the normal group rose with age; the differences in the systolic pressures were less striking. Only 5 per cent. of the rheumatic cases were considered to be hypertensive.

The authors conclude that hypotension [*sic*] is a constant feature of rheumatoid arthritis. They discuss at some length what they consider to be the aetiological implications of their observations, in the light of reports that the use of hypotensive drugs (particularly hydralazine) may precipitate clinical syndromes resembling rheumatoid arthritis, disseminated lupus erythematosus, and scleroderma. *Kathleen M. Lawther.*

Colloidal Gold Sulphide in the Treatment of Rheumatoid Arthritis. (Le sulfure d'or colloïdal dans la thérapeutique de la polyarthrite chronique évolutive.) FORESTIER, J., and THÉVENOZ, F. (1954). *Presse méd.*, **62**, 1056. 1 fig., 1 ref.

The colloidal preparations of gold salts have never proved satisfactory in the treatment of rheumatoid arthritis mainly owing to their low content of metallic salts. A new preparation has, however, recently been introduced in the form of colloidal gold sulphide ("aurolsulfide"), which contains a higher proportion of active gold. This preparation has been found by the authors to be highly effective and in their experience has been better tolerated by the patients than are the "classic gold preparations".

Of 23 patients with chronic rheumatoid arthritis, eleven responded in an extremely satisfactory fashion, seven received appreciable benefit, and only five showed no improvement. In all the cases which benefited the erythrocyte sedimentation rate diminished *pari passu* with the clinical improvement. The authors consider this new preparation of gold to represent an advance in chrysotherapy. *W. S. C. Copeman.*

Observations on the Treatment of Rheumatoid Arthritis by Transfusions of Blood from Pregnant Women. JOSEPHS, C. (1954). *Brit. med. J.*, **2**, 134. 5 refs.

An investigation was undertaken at Staincliffe General Hospital, Dewsbury, Yorkshire, to compare the effects on rheumatoid arthritis of transfusions of blood from pregnant women and of similar transfusions from men and non-pregnant women. Transfusions of 300 ml. were given weekly and the cases followed up for 6 to 18 months.

Of the 53 cases given blood from pregnant donors 19 per cent. are stated to have shown marked subjective and objective improvement, as compared with 13 per cent. of 45 cases receiving blood from men and non-pregnant women.

The author concludes that in rheumatoid arthritis transfusion of blood from pregnant donors produces improvement similar to that resulting from transfusion of blood from non-pregnant donors, but does not produce remissions comparable to those observed during pregnancy. *H. F. Turney.*

How to Prevent Crippling in Rheumatoid Arthritis. KELLY, M. (1954). *Lancet*, **1**, 1158. 5 figs, 12 refs.

Methods of preventing or correcting deformities due to rheumatoid polyarthritis, so that the patient does not become fixed in an armchair posture, are discussed. Flexion of the knee should be prevented by application of a weight-bearing caliper, by quadriceps exercises, and by daily walking. If necessary the joint is manipulated under anaesthesia, the aim being to straighten the knee and to keep the patient walking. As regards hand deformities, a small hand plaster to immobilize only the metacarpo-phalangeal joints is recommended. For inflamed wrist-joints a wrist plaster which allows free finger movements is advocated. It is stated that ankylosis does not develop with this method of treatment.

In the author's view it is a mistake to move a painful joint through a full range of movements daily; moreover, immobilization of a joint for a few weeks does not result in ankylosis. The patient should walk each day and should not be allowed to become bed-ridden. *J. B. Millard.*

Cortisone Acetate *v.* Cortisol in the Treatment of Rheumatoid Disease. WEST, H. F., and NEWNS, G. R. (1954). *Lancet*, **2**, 168.

The authors have compared the effects of cortisone acetate and of cortisol (hydrocortisone "free alcohol") in 22 cases of rheumatoid arthritis under treatment at the Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases. These patients, who had previously received a long-term programme of cortisone acetate treatment, were transferred to cortisol treatment and observed for 3 months. The results were assessed on the basis of physical ability, strength of grip, and erythrocyte sedimentation rate. The authors conclude that cortisol is more potent as an antirheumatic agent than cortisone acetate, but that on the other hand it is more prone to produce undesirable side-effects. *Oswald Savage.*

Comparison of Cortisone and Aspirin in the Treatment of Early Cases of Rheumatoid Arthritis. MEDICAL RESEARCH COUNCIL/NUFFIELD FOUNDATION JOINT COMMITTEE ON CORTISONE, ACTH, AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES (1954). *Brit. med. J.*, **1**, 1223. 4 refs.

In an investigation carried out at six centres in England and Scotland, 61 patients suffering from rheumatoid arthritis and who had developed the disease not more than 9 or less than 3 months previously were treated at random with adequate doses of either cortisone or aspirin. The patients were admitted to hospital for a minimum of 4 weeks, when treatment was initiated. Those treated with cortisone, which was labelled "Tab. (or Mist.) Rheumatic A" and given by mouth, received 300 mg. on the first day; the dose was gradually reduced until the 3rd week, after which "the minimum dosage that would restore maximal functional efficiency without producing serious side-effects" was employed. Patients given aspirin, which was labelled "Tab. Rheumatic C", were started on 6 g. daily, and this too was cut down to a minimum satisfactory dose when possible. At the 12th week drug treatment was gradually withdrawn, and during the 13th week no cortisone or aspirin was given and the patients were observed and investigated. If symptoms recurred the 12 weeks' course of the standard dose was resumed.

Patients were assessed before and at regular intervals during treatment, the assessment including judgment of the patient's functional capacity and of the activity of the disease. Strength of grip, dexterity, joint tenderness, and range of movement were also assessed. Complications, side-effects, and further involvement of new joints were noted and haemoglobin value and erythrocyte sedimentation rate regularly estimated.

Of the 61 patients originally admitted to the trial, three who were being treated with aspirin defaulted, and

two of these cases were regarded as failures of treatment. Of the remaining 58 patients, thirty received cortisone and 28 aspirin. At the end of a year the results were analysed, and it was found that as regards joint tenderness both treatments had had equal effects. The results in regard to range of movement and strength of grip showed that both treatments were about equal in producing an increase of 20 to 30 per cent. of movement and one of 40 to 50 per cent. in strength of grip. Similarly, both treatment groups showed equal improvement in dexterity, but in respect of haemoglobin level and erythrocyte sedimentation rate there was a significantly greater improvement in the group treated with cortisone. Clinical assessment showed a remarkable similarity between the two treatment groups; minor complications of treatment were also equally distributed between the two groups.

It is envisaged that the trial will continue into a second and third year.

[It is important to realize that this investigation covers only one aspect of the comparison between the efficacy of cortisone and of aspirin in rheumatoid arthritis. The study was not of a wide series of patients suffering from rheumatoid arthritis at all stages, but was confined to a small group of sufferers in the early stages of the disease.]

W. Tegner.

Treatment of Rheumatoid Arthritis with Multi-Articular Local Injections of Hydrocortisone Acetate. (Traitement de la polyarthrite chronique évolutive par les injections locales multi-articulaires d'acétate d'hydrocortisone.) WEISMANN-NETTER, R., LÉVY, R., and LORCH, P. (1954). *Presse méd.*, **62**, 852. 1 ref.

The authors, working at the Hôpital Beaujon, Paris, treat rheumatoid arthritis by multiple intra-articular injections of hydrocortisone acetate under general anaesthesia. Depending on the size of the joint, 10 to 100 mg. of hydrocortisone is injected into each of the affected joints at one session. The total dose of several hundred mg. given has not produced any of the side-effects associated with systemic therapy with adrenal hormones. Depending on the result, the treatment may be repeated two or three times at weekly intervals; there has been no apparent loss of effect with repeated injections, and improvement has been maintained for periods varying from a few weeks to several months. The authors prefer this method to daily injections of two or three joints under local analgesia as it saves time and is considered to be less disagreeable to the patient.

Of seven cases of advanced rheumatoid arthritis treated by this method after failure to response to other therapy, including administration of cortisone and ACTH, three showed marked improvement, three were moderately improved, and one did not respond; the cause of failure in this last case was considered to be insufficient dosage. In view of the absence of side-effects and the encouraging results obtained, the authors consider this to be one of the best methods of treatment of rheumatoid arthritis so far available.

[Seven cases is too small a series upon which to base any assumption, but further work is continuing.]

F. Clifford Rose.

Frequency and Significance of Amyloid Changes in Rheumatoid Arthritis. [In English.] TEILUM, G., and LINDAHL, A. (1954). *Acta med. scand.*, **149**, 449. 3 figs, 13 refs.

The incidence and significance of amyloid changes in rheumatoid arthritis was investigated at the University Institute of Pathological Anatomy, Copenhagen. Using methyl violet as a stain for sections of tissue obtained at necropsy in 28 cases of rheumatoid arthritis, the authors found amyloid deposits in seventeen, the amyloidosis being moderately severe or severe in ten. The deposits were most pronounced in the kidneys, spleen, and adrenal glands, but were also found in the liver, myocardium, and intestine. Vessel walls were frequently involved. Albuminuria was present in thirteen of the seventeen cases in which amyloidosis was found, and uraemia was the cause of death in seven of the 28 cases. Amyloidosis was diagnosed clinically in only one case, and only in two was the condition recognized macroscopically at necropsy.

A. Wynn Williams.

Contribution to the Oral Gold Therapy of Rheumatism. (Beitrag zur peroralen Goldtherapie des Rheumatismus.) SCHREINER, B., and STEPHANTSCHITZ, G. (1954). *Medizinische*, **33/34**, 1112. 6 refs.

The authors maintain that gold still plays a valuable role in the treatment of rheumatoid arthritis and that there is room for new preparations of low toxicity. They have recently observed at the University Medical Clinic, Graz, Austria, the effects of a complex preparation, "aurubin", containing gold salts among a number of other constituents and which can be taken by mouth, in the treatment of various rheumatic conditions, mostly rheumatoid arthritis. In this disease its effects were less obvious in cases of recent onset than in more chronic cases; in eleven out of 35 of the latter with sufficient follow-up improvement was noted within 4 to 7 days. Side-effects (mainly nausea and diarrhoea) were encountered in eight cases, but there was no occurrence of leucopenia, albuminuria, or haematuria. Excretion of 17-ketosteroids was unaffected and no change was observed in the number of circulating eosinophil leucocytes. It is assumed that gold is the active principle in this complex preparation, but its mode of action has yet to be elucidated and further studies are in progress.

D. Preiskel.

Rheumatoid Arthritis-like Syndrome during Apresoline Therapy. Report of a Case. BEELAR, V. P. (1953). *Med. Ann. Distr. Columbia*, **22**, 651, 696. 2 refs.

Multi-Articular Injections of Hydrocortisone, the Treatment of Choice in Rheumatoid Arthritis. (Les injections multi-articulaires d'hydrocortisone, traitements de choix de la polyarthrite chronique évolutive.) WEISMANN-NETTER, R., KREWER, B., and LORCH, P. (1954). *Rev. argent. Reum.*, **19**, 149. 3 refs.

Pancytopenia associated with Rheumatoid Arthritis—Felty's Syndrome. Treatment with Cortisone and Splenectomy. VAN SLYCK, E. J. (1954). *J. Mich. med. Soc.*, **53**, 735. 2 figs, 9 refs.

Still's Disease as an "Adaptation" Syndrome. (Zur Ätiologie der infantilen Still'schen Erkrankung im Sinne einer "Adaptation".) MAYERHOFER, E. (1954). *Ann. paediat. (Basel)*, **183**, 203. 21 refs.

Rheumatoid Arthritis. Need for Individualized Therapy. ROGOFF, B. (1954). *Missouri Med.*, **51**, 1001.

Pneumoconiosis and Rheumatoid Arthritis (Caplan's syndrome). [In English.] VAN DER MEER, C. (1954). *Ned. T. Geneesk.*, **98**, 3539. 2 figs, 12 refs.

Surgical Intervention in Rheumatoid Arthritis. [In English.] BOESMAN, T. (1954). *Ned. T. Geneesk.*, **98**, 3545. 5 figs, 7 refs.

Theoretical and Practical Aspects of Rheumatoid Arthritis developing after the Age of Sixty. (Quelques aspects théoriques et pratiques de la polyarthrite chronique évolutive survenant après la soixantaine.) CHAPUIS, R. (1954). *Rev. méd. Suisse rom.*, **54**, 603. 17 refs.

Chronic Rheumatoid Arthritis: Psycho-Social Factors in Rehabilitation. LOWMAN, E. W., LEE, P. R., MILLER, S., KING, R., and STEIN, H. (1954). *Arch. phys. Med.*, **35**, 643.

(Osteo-Arthritis)

Osteo-Arthritis and Rest. HART, F. DUDLEY, WATKINS, M., BURLEY, D., and RICHARDS, M. T. (1954). *Brit. med. J.*, **2**, 269. 11 refs.

The authors point out that in articles and textbooks dealing with the treatment of osteo-arthritis the value of rest is nearly always emphasized but its hazards are rarely mentioned. They agree that excessive use of an affected joint will produce a sharp reaction within 24 to 48 hours, but hold that immobilization may produce much more prolonged disability. When elderly patients are rested in bed as part of the treatment of cardiac decompensation, bronchitis, pneumonia, bleeding peptic ulcer, or other diseases, they may develop for the first time joint symptoms associated with osteo-arthritis, or existing symptoms of osteo-arthritis of the hips or knees may be severely aggravated. The histories of four such patients admitted to St. Stephen's Hospital, London, are described to illustrate this point.

Harrison and others (*J. Bone Jt Surg.*, 1953, **35B**, 598) have emphasized "the necessity for use and compression of cartilage in order to maintain its continued health", while Lloyd-Roberts (*J. Bone Jt Surg.*, 1953, **35B**, 627) has pointed out the effect of fibrosis and shortening of the capsule in the production of symptoms in osteo-arthritis of the hip. Those two findings together help to explain the deterioration which occurs in a patient's weight-bearing joints during a period of complete rest in bed, when there is a tendency for the hip to be held in flexion and lateral rotation, while the knee is also flexed. In order to prevent the adverse changes which follow long-continued maintenance of this position the authors suggest that patients should spend part of the day lying flat, and selected patients with flexion deformities already present should be induced to spend periods in the prone position. Exercise of the hips, knees, and ankles should be undertaken as soon as possible. Analgesics should be used freely if pain prevents proper co-operation in the performance of these exercises, while the injection of a local analgesic into ligamentous attachments or the intra-articular injection of hydrocortisone may be useful in helping to mobilize stiff and painful knees. *C. E. Quin.*

Osteo-Arthritis in the Aged. KUHNS, J. G. (1954) *J. Amer. Geriat. Soc.*, **2**, 519. 12 refs.

Neurologic Complications of Osteo-Arthritis of the Cervical Spine. NEUWIRTH, E. (1954). *N.Y. St. J. Med.*, **54**, 2583. 4 figs, 45 refs.

Tissue Therapy in Osteo-Arthrosis. [In English.] LINDHOLM, R. V. (1954). *Ann. Chir. Gynaec. Fenn.*, **43**, Suppl. 5, 214. 5 refs.

Present Position of Arthroplasty of the Hip in Rheumatism. (État actuel des arthroplasties de la hanche dans le rhumatisme.) HERBERT, J. J. (1954). *Rev. Rhum.*, **21**, 556. 4 figs, 5 refs.

Nosological and Pathogenetic Identity of Heberden's Nodes and the Dactylo-Trachelo-Arthrotic Syndrome. (Sull'autonomia nosologica e patogenetica dei noduli di Heberden: la sindrome dattilo-trachelo-artrosica.) ROVERSI, A. S., and MARS, G. (1954). *Reumatismo*, **6**, 221. 9 figs, 48 refs.

Pathogenesis of Osteo-Arthritis. (Le début de la maladie arthrosique.) JUSTIN-BESANÇON, L. (1954). *Reumatismo*, **6**, 329.

Studies in Experimental Osteophytosis. (Etudes sur l'ostéophytose expérimentale.) LACAPÈRE, J., DELAVILLE, G., and DRIEUX, H. (1954). *Rev. Rhum.*, **21**, 639. 1 fig.

Treatment of Osteo-Arthritis of the Hip. (Zur Behandlung der Arthrosis deformans des Hüftgelenks.) KIBLER, M., and SCHIMMEL, A. (1954). *Dtsch. med. Wschr.*, **79**, 1824. 7 refs.

Osteo-Arthritis of the Sterno-Costo-Clavicular Joint. (L'artrosi deformante dell'articolazione sterno-costo-clavicolare.) BONOLA, A., and MASTRAGOSTINO, S. (1954). *Reumatismo*, **6**, 333. 10 figs, 17 refs.

Conservative Orthopaedic Treatment of Osteo-Arthritis. KUHNS, J. G. (1954). *Rheumatism*, **10**, 85. 4 figs.

Climacteric Arthroses. (Die klimakterischen Arthrosen.) SCHEUER, F. (1954). *Münch. med. Wschr.*, **96**, 1156.

(Spondylitis)

Ocular Manifestation of Ankylosing Spondylitis. (Les manifestations oculaires de la spondylarthrite ankylosante.) MICHAUD, P., and FORESTIER, J. (1954). *Rev. Rhum.*, **21**, 489. 19 refs.

The ocular manifestations of ankylosing spondylitis are in general confined to the uvea. The reported incidence of uveitis has varied widely. In the authors' series of 200 cases of ankylosing spondylitis uveitis was seen in seventeen cases (8·5 per cent.); in this group no other eye affection, such as the Gougerot-Sjögren syndrome, was observed. They point to the great rarity of uveitis in rheumatoid arthritis, and are convinced that uveitis and spondylitis are manifestations of the same morbid process.

The symptomatology of uveitis is discussed. Attacks may be repeated at intervals for some years before the appearance of the first somatic symptoms of spondylitis, and they often occur in the early pre-ankylosing phase of the disease. It is particularly important, therefore, when confronted with a case of uveitis in a young man, even if it is accompanied only by vague "rheumatic" pains, to remember this possibility and investigate the radiological appearances of the sacro-iliac joints. The clinical forms of uveitis, which vary in severity and gravity, are fully described. The benign form is liable to be mistaken for conjunctivitis; it manifests itself by slight symptoms and signs or iritis, very slight pain, some photophobia and lachrymation, and a sluggish pupil reaction, but usually abates spontaneously in 8 to 10 days. In more marked attacks there is some pericorneal injection, and some fragile synechiae may form. More severe is the typical form, an acute diffuse uveitis, of sudden onset. Here there is marked photophobia, with the usual signs of inflammation of the iris, but only a slight tendency to the formation of posterior synechiae. These attacks also generally subside fairly quickly, leaving no residual signs, but in rare cases may progress to a more severe form resulting in total uveitis, with severe pain, marked signs of iritis, and affection of the vitreous. During the following 6 to 8 weeks the condition slowly abates, although some posterior synechiae persist. Much more severe are the granulomatous forms of uveitis; these follow recurrences of simple iritis, are characterized by a tendency to form tough posterior synechiae, and nodules may be observed in the iris. The most serious of all, however, is torpid uveitis, which begins quietly, with mild symptoms, and progresses chronically and insidiously over months or years, with the formation of very strong synechiae, which by occluding the pupil may lead to total blindness.

The treatment is discussed. In the authors' practice, to obtain and maintain pupillary dilatation, atropine is always combined with repeated instillations of cortisone. If this fails, subconjunctival injections of cortisone and adrenaline are tried; in still more resistant cases hyaluronidase is given in addition. In severely painful attacks the authors advise the early retrobulbar injection of 1 to 2 ml. 40 per cent. alcohol. *Kenneth Stone.*

Sacro-Iliitis. (Sacro-iliites.) VIEIRA, J. A. N. (1954). *Gaz. med. port.*, **7**, 581. 6 figs, 20 refs.

Infective Spondylitis. (Espondilitis infecciosas.) BARCELÓ, P., and VILASECA, J. M. (1954). *Reumatismo*, **6**, 267.

(Miscellaneous)

Relationship between Scapulo-Humeral Peri-Arthritis and Coronary Disease. (Contributo allo studio dei rapporti tra periartrite scapulo-umerale e malattie delle coronarie.) VECCHI, G. P., and RUBBIANI, V. (1954). *Minerva med.* (*Torino*), **2**, 755. 25 refs.

The occurrence of pain and limitation of movement in the shoulder in patients suffering from coronary ischaemia is well recognized. In this paper from the University Medical Clinic, Modena, the authors describe six typical cases to illustrate the clinical features and report an attempt to determine whether patients complaining primarily of symptoms of scapulo-humeral periarthritis present any evidence of coronary insufficiency.

In a series of 48 such patients, ranging in age from 27 to 68, electrocardiography showed that nine had definite evidence of coronary insufficiency, while a further ten suffered from lesser degrees of myocardial damage. Few of these patients had symptoms referable to the cardiovascular system, but since the electrocardiogram was abnormal in nearly 40 per cent. of them it is suggested that the heart should be carefully investigated in all such cases. Two reasons are given for the association of these lesions:

(1) the similarity of the sympathetic nerve supply to the shoulder and the heart;
(2) the fact that the connective tissue and vascular structures in the myocardium, shoulder, thyroid gland, and gall-bladder have a common developmental origin.

As might be expected, therefore, periarthritis of the shoulder is also often associated with thyrotoxicosis and cholecystitis.

[Unfortunately, no comparable electrocardiographic findings are given for a group of patients of the same age distribution not suffering from scapulo-humeral peri-arthritis.] *A. Paton.*

Alimentary Tract in Disseminated Scleroderma with Emphasis on Small Bowel. ABRAMS, H. L., CARNES, W. H., and EATON, J. (1954). *Arch. intern. Med.*, **94**, 61. 6 figs, 36 refs.

After a brief review of the literature the authors, from Stanford University School of Medicine, San Francisco, report six cases of scleroderma in which, in addition to the well-recognized oesophageal lesions, there were widespread lesions of the intestinal tract. These involved the duodenum, jejunum, and ileum, and their presence was suggested clinically by anorexia, abdominal pain, and loss of weight. Radiological examination revealed alteration in the calibre (dilatation), tone, peristalsis, and motility of the affected bowel. The cases are illustrated by excellent reproductions of radiographs and of photomicrographs of post-mortem material.

In three of the six cases the course was rapidly progressive, death occurring within 2 years of the onset of symptoms. The characteristic finding at necropsy in

these cases was loss of muscle fibres in the muscularis without appreciable replacement by fibrous tissue.

Treatment with cortisone or corticotrophin produced a temporary remission in two other cases, and in the remaining case resection of the oesophagus and gastroenterostomy were performed for the relief of dysphagia.

Nigel Compston.

Investigation of Synovial Exchange by means of Radioactive Sodium (^{24}NA). (Les échanges synoviaux. Leur mesure à l'aide du radio-sodium Na^{24}.) COSTE, F., BOUREL, M., and MOREL, F. (1954). *Ann. Méd.*, **55**, 360. 12 figs, 31 refs.

Writing from the Rheumatological Clinic, Faculty of Medicine, Paris, the authors describe a method for the measurement of synovial exchange in which, after injecting radioactive sodium (^{24}Na) in an isotonic solution intra-articularly, they record its disappearance from the joint by means of a Geiger-Müller counter to which is attached a graphic recorder; this method has the advantage over those used previously in that the injection does not interfere with normal metabolism. It was found that in animals of the same species and age, the graph obtained obeyed constant laws.

Sodium permeability depends upon two factors—the state of the connective tissues and the blood supply—and one or other of these was varied in the study here reported of synovial exchange in the knee-joint of the rabbit. The connective-tissue barrier was altered by injections of testicular hyaluronidase, and as expected, the clearance of ^{24}Na was more rapid. The blood supply was altered either by femoral arteriectomy, when the clearance was less, even after the injection of hyaluronidase; or by the injection of vasodilator substances when, however, the results were equivocal after administration of acetyl-β-methylcholine, and no alteration in synovial clearance was found when sodium nicotinate was given.

The synovial exchange was also measured after inflammation in the joint had been produced by repeated intra-articular injections of ethanolamine oleate, the effect of steroids on the exchange taking place in the inflamed joint being then ascertained. It was found that systemic administration of cortisone or intra-articular injection of deoxycortone acetate or hydrocortisone slowed down exchange when this was initially rapid, and increased it when it was initially slow. The authors stress that since the experimentally induced inflammatory reaction altered the basic structure of synovial connective tissue, the results obtained in this study are not necessarily applicable to inflamed joint conditions in the human patient.

F. Clifford Rose.

Treatment of Chronic Arthritis with a Combination of Cobra Venom, Formic Acid, and Silicic Acid. BRYSON, K. D. (1954). *Amer. Surg.*, **20**, 751. 2 refs.

The author describes the treatment of a series of 466 consecutive cases of chronic arthritis (excluding 150 in which the course was not completed) with "nyloxin", a preparation containing cobra venom, formic acid, and silicic acid, given by subcutaneous injection in doses increasing from 1 to 3 ml. Treatment was usually given at weekly intervals at first, then less frequently as control of symptoms was obtained, until eventually in most cases the patient received only a maintenance injection every 3 months. The patients are classified in three broad diagnostic groups—osteo-arthritis, rheumatoid arthritis, and mixed types—the numbers in these groups being 344, 74, and 48 respectively. The results as assessed by the physician after consideration of all the relevant factors were "satisfactory" in 426 cases (91·4 per cent.) and "unsatisfactory" in forty (8·6 per cent.). The patients' own opinions on their condition before, during, and after treatment are analysed separately and here again the results show a high proportion of successes; for instance, of 94 patients reporting 6 months to 5 years after cessation of treatment, 88 (93·6 per cent.) said that their condition remained satisfactory. The author also notes that the patients' general health was improved, often with a rise in the haemoglobin level, and that hypertension, where present, was reduced.

[It is unfortunate that insufficient clinical details are given in this paper to enable the reader to assess the value of this treatment.] *K. C. Robinson.*

Evaluation of the Bryson Treatment of Arthritis. LUMPKIN, W. R., and FIROR, W. M. (1954). *Amer. Surg.*, **20**, 756. 2 refs.

An investigation was carried out at the Maryland General Hospital, Baltimore, into the claims of Bryson (see Abstract on this page) that a mixture of cobra venom and silicic and formic acids was effective in the treatment of chronic arthritis. Three solutions were prepared for subcutaneous injection:

(A) containing formic acid only;
(B) containing all three ingredients in the proportions used by Bryson;
(C) a mixture of formic and silicic acids.

The patients, who were classified as having either rheumatoid or hypertrophic arthritis (the latter predominating), were given weekly injections of one or other of these preparations in increasing doses, the interval being later extended gradually as described by Bryson.

The results were as follows:

Ten patients had Solution A, and one responded;
61 had Solution B, and 52 responded;
Ten had Solution C, and eight responded (though the degree of improvement was thought to be less than with Solution B).

A response was defined as the subsidence or cessation of pain, swelling and stiffness in the affected joints, and improvement in general health. The authors conclude that Bryson's treatment gives substantial relief of symptoms in more than 80 per cent. of cases of chronic arthritis. *K. C. Robinson.*

Effect of Mepacrine on Light Sensitivity in Lupus Erythematosus. BETTLEY, F. R., and PAGE, F. (1954). *Brit. J. Derm.*, **66**, 287. 6 figs, 2 refs.

The investigation described in this paper from the Middlesex Hospital, London, was undertaken to determine whether the beneficial effect of mepacrine in chronic

lupus erythematosus is the result of an increase in tolerance to light. Patients with chronic lupus erythematosus received up to 100 mg. mepacrine twice a day, and the sensitivity of the skin to light was tested monthly. A commercial "sun lamp" with a filter of cellulose acetate was used to test light sensitivity, a photometer being employed to ensure accuracy of dosage. The minimum erythema dose (M.E.D.) was measured on the skin of the abdomen.

The average M.E.D. in untreated patients with lupus erythematosus was about half the normal. In patients receiving mepacrine the increase in light tolerance was very gradual but the clinical effect on the lesions of lupus erythematosus was more rapid. The authors believe the results indicate that "mepacrine has another action which exerts a more immediate effect on the disease itself than simply by increasing tolerance to sunlight".

[The conclusions reached would be more impressive if the findings were considered statistically. Averaged results from five control subjects and nine patients with lupus erythematosus after one-half or one-quarter minute's exposure cannot be assessed satisfactorily in any other way.] *S. T. Anning.*

Lupus Erythematosus. Treatment by Combined Use of Massive Amounts of Pantothenic Acid and Vitamin E. WELSH, A. L. (1954). *Arch. Derm. Syph.* (*Chicago*), **70**, 181. Bibl.

The literature on the metabolic functions of pantothenic acid and vitamin E (α tocopherol) is reviewed at length, and the results of the use of these compounds in the treatment of lupus erythematosus are summarized. The author believes that many of the failures have been due either to the fact that these vitamins were administered individually instead of in combination, or to inadequate dosage.

To 67 patients suffering from lupus erythematosus massive doses of pantothenic acid combined with α tocopherol were given, the treatment schedule being 10 to 15 g. calcium pantothenate daily, 10 to 15 g. pantothenyl alcohol daily, and 5 to 10 g. sodium pantothenate daily, combined with 3 to 6 g. daily of a mixture of three tocopherols. In a group of 36 patients with chronic discoid lupus erythematosus objective improvement was observed in 4 to 6 months; in half the patients the condition had cleared completely and in the remainder it was much improved at the time of reporting. Similar results were obtained in a group of seventeen patients with disseminated discoid lupus erythematosus, improvement being noted after 2 months, and in eleven with the subacute disseminated form of the disease, the response in this group being rapid, usually after one month. In three cases of acute disseminated lupus erythematosus treatment was started while the acute phase was being brought under control with steroid hormones; by administration of pantothenic acid and tocopherol the patients were maintained without relapse for 7, 11, and 19 months respectively. In general, it was noted that the more hypertrophic and infiltrated the process the slower the response. Apart from transient nausea and gastric distress there were no complications, and there were no abnormal findings in the blood or urine of patients treated for 1 to 3 years.

Discussing the results, the author suggests that as α tocopherol may be metabolized in the body to furnish precursor "cortisone-like materials", and pantothenic acid is related to the secretion and formation of steroid hormones—a theory supported by the functional inadequacy of the adrenal cortex in pantothenate deficiency —massive doses of pantothenic acid with α tocopherol enables the body slowly to synthesize a cortisone-like compound. *Benjamin Schwartz.*

Nitrogen Mustard in Treatment of Systemic Lupus Erythematosus. DUBOIS, E. L. (1954). *Arch. intern. Med.*, **93**, 667. 9 refs.

Following claims that nitrogen mustard is of value in the treatment of glomerulonephritis and also in that of systemic lupus erythematosus with renal involvement, the author studied the effect of this form of therapy and of treatment with triethylene melamine in twenty cases of the latter disease.

None of the patients was treated until the maximum possible benefit had been obtained with cortisone, and this steroid was administered throughout the trial. No improvement was noticed in five patients suffering from active disease without apparent renal involvement, nor in four with or without overt renal disease in whom there was established hypertension. Considerable improvement was observed, however, in the group of patients suffering from "nephrotic nephropathy". The greater the degree of oedema and albuminuria, the greater was the response to treatment. All twenty patients were given nitrogen mustard intravenously in a single dose of 20 mg. in a dextrose infusion. In successful cases a diuresis occurred within 3 to 14 days. No serious toxic effects were observed.

Triethylene melamine was given to five of the patients in a total dose of 10 to 15 mg. over a 2- to 3-day period. In one of them agranulocytosis developed and in another a fatal aplastic anaemia. It was not used further because of its unpredictable behaviour in this disease.

Nigel Compston.

Trial of a Synthetic Antimalarial Derivative of Quinoline in the Treatment of Chronic Rheumatism. (Essais de traitement des rhumatismes chroniques par un antimalarique de synthèse dérivé de la quinoléine.) LACAPÈRE, J., MONIER, H., and VIAL, G. (1954). *Rev. Rhum.*, **21**, 389. 11 refs.

Reports of the successful treatment of lupus erythematosus with the synthetic antimalarial compound mepacrine, and later with the less toxic compound chloroquine, prompted a trial of the latter drug in rheumatoid arthritis. The authors find that a dose of 100 to 200 mg. chloroquine per day produces only minimal toxicity, causing at most slight nausea, loss of appetite, or tinnitus. With a dose of 300 to 450 mg. daily, however, intolerance is more common.

In 46 cases of rheumatoid arthritis the drug had a beneficial effect, which was in marked contrast to the absence of any effect in 25 control cases of radicular pain

and nineteen of osteo-arthritis, improvement, apparent on the 15th day, being noted in approximately two-thirds of the former group. The erythrocyte sedimentation rate also fell, but not in proportion to clinical improvement.

The average dose was 100 to 150 mg. each morning for the first 3 to 10 days, after which a second dose of 100 to 150 mg. was added in the evening. If well tolerated, this dosage was continued for 4 to 6 weeks, but if symptoms of intolerance—loss of appetite, nausea, vertigo, tinnitus, or paralysis of accommodation—appeared, it was reduced to 100 mg. daily and continued for 2 to 3 months. *Kenneth Stone.*

Trial of Synthetic Antimalarial Drugs in the Treatment of Inflammatory Rheumatism. (Essai de traitement des rhumatismes inflammatoires par les antimalariques de synthèse.) FORESTIER, J., and CERTONCINY, A. (1954). *Rev. Rhum.*, **21**, 395. 5 refs.

Since it was first observed in 1951 that associated joint symptoms improved during the treatment of lupus erythematosus with mepacrine, several observers have reported improvement in cases of rheumatoid arthritis as a result of treatment with either mepacrine or chloroquine. The present authors have used both substances, but find that tolerance to chloroquine is decidedly greater than to mepacrine. Only three of eleven patients given mepacrine failed to show symptoms of intolerance, whereas of seventeen patients given chloroquine, only one had to stop taking the drug because of digestive disturbance. As the effect of the two drugs on the rheumatic condition appeared the same, the use of mepacrine has therefore been abandoned.

The dosage used in either case was 0·1 g. twice daily for 20 days in each month for periods varying from 1 to 6 months. Of eleven cases of rheumatoid arthritis treated with mepacrine and seventeen with chloroquine, about one-half showed improvement, with reduction in pain and joint swelling, increased activity, and often a fall in the erythrocyte sedimentation rate. But only one of three patients with ankylosing spondylitis appeared to derive benefit. *Kenneth Stone.*

Tennis-elbow (Epicondylalgia Externa). Treatment with Hydrocortisone. QUIN, C. E., and BINKS, F. A. (1954). *Lancet*, **2**, 221. 9 refs.

Tennis-elbow treated with Hydrocortisone Acetate. MURLEY, A. H. G. (1954). *Lancet*, **2**, 223. 13 refs.

Hydrocortisone in Tennis-elbow. FREELAND, D. E., and GRIBBLE, M. DE G. (1954). *Lancet*, **2**, 225. 5 refs.

The work described in these three papers was aimed at assessing the value of hydrocortisone in the treatment of the condition known as tennis elbow. There are numerous references to the literature concerning the histopathology of the syndrome, and some emphasis is laid upon the ineffectiveness of the many methods of treatment hitherto employed, with the single exception of surgery, which, though effective, is a rather major undertaking for a relatively minor complaint that in any case spontaneously recovers in due course. Quin and Binks present the results in 31 cases, with much clinical information. They were not convinced that trauma was a significant aetiological factor, and were impressed with the fact that there was often a history of "aches and pains in other parts of the body", suggesting that the condition is a manifestation of a more generalized disturbance. Pain is aggravated by gripping and dorsiflexion of the wrist. Murley notes that the condition commonly affects those over 30 years of age who undertake unaccustomed activities involving repeated pronation and supination while the hand is gripping.

The authors of all three papers compare the effect of hydrocortisone with that of procaine, another commonly used method of treatment. Quin and Binks injected procaine at the maximum point of tenderness and then injected varying amounts of hydrocortisone into the identical spot. The authors of the other two papers injected 25 mg. hydrocortisone alone into the area of maximum tenderness; or, in their control series, 1 ml. 2 or 5 per cent. procaine respectively. Results were assessed at definite intervals afterwards. Quin and Binks recorded 26 successful results from a single injection (combined procaine and hydrocortisone). Of the five cases in which this treatment was a failure two responded after a second injection. Various reactions are described. Murley records fourteen successful results and five failures out of nineteen cases. Subsequent relapses were common, but responded to further injections; no patient was made worse. Of the eighteen patients treated with procaine alone as a control "a few found their symptoms improved but most were unrelieved". Freeland and Gribble, on the basis of sixteen injections in fourteen cases, conclude that "the local injection of hydrocortisone . . . was no more or less effective in curing tennis-elbow than a similar injection of 5 per cent. procaine". They express surprise that procaine, being only a short-lasting local analgesic, produced such a clear and long-lasting improvement at all. [Such a view overlooks the other pharmacological actions of this substance. There is perhaps some doubt about the advisability of using procaine as a control injection in such cases as these, as it is known to have some degree of effectiveness in the treatment of this condition.]

The only deduction to be made from consideration of the three papers together is that Freeman and Gribble obtained equally effective results from hydrocortisone and 5 per cent. procaine, while Murley, using only 2 per cent. procaine, failed to observe any effective response in the patients so treated, which seems to indicate that procaine may be as effective as hydrocortisone provided it is used in sufficient concentration.

Harry Coke.

Intra-Articular Injection of Hydrocortisone Acetate. (Intra-articulaire toediening van hydrocortisonacetaat.) KUIPERS, R. K. W. (1954). *Ned. T. Geneesk.*, **98**, 1558. 3 refs.

After discussing briefly the information that may be obtained by joint puncture and examination of the punctate as an aid to diagnosis in arthritic conditions, the author describes his experience in private practice with the intra-articular injection of hydrocortisone acetate. A dose of 25 mg. (or 10 mg. for the smaller joints) for

five to ten injections per case produced satisfactory results, as judged 4 weeks after completion of treatment, in 75 per cent. of 160 patients with various forms of rheumatic joint disease. Improvement was judged by lessening of the pain, stiffness, and inflammation, which was generally accompanied by simultaneous improvement in the condition of the punctate. The response was better in osteo-arthritic conditions (60 per cent.) of patients improved) than in rheumatoid arthritis; in humero-scapular periarthritis, however, the results were generally inferior to those obtained by intravenous infusion of ACTH. The best results were seen in monarthritic conditions and in cases in which one or two joints in polyarthritis proved resistant to systemic treatment with gold or cortisone. The technique of injection of the joints presented no particular difficulties.

R. Crawford.

Oral Cortisone Therapy in Peri-Arthritis of the Shoulder. A Controlled Trial. BLOCKEY, N. J., WRIGHT, J. K., and KELLGREN, J. H. (1954). *Brit. med. J.*, **1**, 1455. 6 refs.

At the Manchester Royal Infirmary the effect of cortisone was compared with that of an inert substance in treating 32 cases of periarthritis of the shoulder. The patients, all between 20 and 70 years of age, had periarthritis of one or both shoulders without radiological evidence of bone or joint disease and in all of them the erythrocyte sedimentation rate was normal; those with symptoms or signs of generalized arthritis were excluded. Half the patients were given a suspension of cortisone by mouth for 4 weeks and the other half received an inert suspension in the same amount, the latter being indistinguishable in both appearance and taste from the cortisone suspension.

All patients were instructed in shoulder exercises, and at the end of 4 weeks the shoulders of those who had not progressed satisfactorily were manipulated under general anaesthesia. It was found that although some of the patients receiving cortisone had less pain before and after manipulation than the control group and fewer required restoration of movement under anaesthesia, some patients were not helped by the hormone. No statistical difference was observed between the results in the two groups. *Oswald Savage.*

Importance of Bottyán's Antigen in Ophthalmology. PALIĆH-SŻANTÓ, O. (1954). *Proc. XVII int. Cong. Ophthal.* (*Montreal-New York*).

The Bottyán test is of great value in the diagnosis of dental foci of infection in ocular disease. The Bottyán antigen does not contain bacteria and is not toxic. In eye diseases caused by syphilis or tuberculosis the test is negative. Where there is a positive Bottyán test a rheumatic aetiology must be considered even when there is not rheumatic illness and no history of rheumatic illness. *Official Abs.* (*abridged*).

Sjögren's Syndrome. MACLEAN, K., and ROBINSON, H. S. (1954). *Canad. med. Ass. J.*, **71**, 597. 20 refs.

A 67-year-old woman had suffered from severe arthritis for 17 years. Besides the stigmata of severe arthritis, she showed dry corneae, conjunctiva, mouth, and throat, and a depression at the angle of the jaw, corresponding to the region of parotid glands. A sialogram of the right parotid gland presented a picture suggestive of parenchymal atrophy. Gastric anacidity was reduced. She was anaemic and one test showed L.E. cells in the peripheral blood. *C. McCulloch.*

Arthritis with Simultaneous Suppurative Conjunctivitis and Urethritis (the so-called Reiter Syndrome) treated with Post-Insulin Light Hypoglycaemic States. (In Polish.) DAWIDOWICZ, A. (1953). *Pol. Tyg. lek.*, **8**, 1700. 14 refs.

Case report of a 35-year-old man who had two onsets of Reiter's syndrome with a 15-year interval. The aetiology could not be determined. He was given post-insulin light hypoglycaemic "states" with good results. *W. H. Melanowski.*

Complete Reiter's Syndrome. (Syndrome de Reiter complet.) SYLVESTRE, L. (1953). *Union méd. Canada*, **82**, 928.

The patient, shortly after his marriage, developed urethritis, arthritis, and conjunctivitis. "Pleuro-pneumonia-like-organisms" were cultured from the urethra. *C. McCulloch.*

Quinacrine (Atebrin) in Treatment of Systemic and Discoid Lupus Erythematosus. DUBOIS, E. L. (1954). *Arch. intern. Med.*, **94**, 131. 19 refs.

Arthritis associated with Non-Gonococcal Urethritis. HARKNESS, A. H. (1954). *Rheumatism*, **10**, 91. 5 figs, 8 refs.

Reiter's Syndrome. (Le syndrome de Reiter.) FOREST, A. (1954). *Rev. Rhum.*, **21**, 517. Bibl.

Pathogenesis of Sjögren's Syndrome. (Zur Pathogenese des Sjögren-Syndroms.) GAMP, A. (1954). *Z. Rheumaforsch.*, **13**, 221. 1 fig., 18 refs.

Gougerot-Sjögren Syndrome. (Le syndrome de Gougerot-Sjögren.) OFFRET, G., and MASSIN, M. (1954). *Rev. Rhum.*, **21**, 463. Bibl.

Antirheumatic Agents and the Erythrocyte Sedimentation Rate. (Médicaments antirhumatismaux et vitesse de sédimentation globulaire.) BONARD, E. C., and SCHEIDEGGER, J. J. (1954). *Rev. Rhum.*, **21**, 651. 2 figs, 29 refs.

Tuberculin Arthritis of the Guinea-Pig and its Modification by Certain "Anti-inflammatory" Agents. (L'arthrite tuberculinique du cobaye et ses modifications sous l'effet de certains médicaments dits "anti-inflammatoires".) ARLET, J., DELAUDE, A., and CASTAIGNE, A. (1954). *Rev. Rhum.*, **21**, 676. 7 figs.

Acute Primary Rheumatic Thyroiditis. (Über akute primär-rheumatische Thyreoditis.) DANOPOULOS, E., and MELISSINOS, K. (1954). *Dtsch. med. Wschr.*, **79**, 1729. 6 refs.

Treatment of Acromio-Clavicular Arthrosis. [In English.] ARONSSON, H. (1954). *Acta chir. scand.*, **107**, 589. 3 figs, 8 refs.

Intravenous Adrenaline in Minute Doses in Rheumatology. (Adrénaline intraveineuse en microdoses en rhumatologie.) ARSOV, D. (1954). *Brux.-méd.*, **34**, 1731. 5 figs.

Bone and Joint Changes in Psoriasis. (Le alterazioni ossee ed articolari degli psoriatici.) COSTA, F., and PAPAGNI, L. (1954). *Reumatismo*, **6**, 304. 12 figs, bibl.

Psoriatic Arthropathy. (Le artropatie psoriasiche.) ALLARIA, A., and FRANZ, A. (1954). *Reumatismo*, **6**, 373. 5 figs, bibl.

Idiopathic Crural Radiculalgie. (Radiculalgies crurales idiopathiques.) SÈZE, S. DE, WELFLING, J., and JURMAND, S.-H. (1954). *Rev. Rhum.*, **21**, 635.

Periosteal Proliferation in the Radiographic Appearance of Chronic Joint Disease. Its Diagnostic and Pathogenetic Significance. (La proliferazione periostea nel quadro radiologico dell'artrosi. Sua importanza diagnostica ed interpretazione patogenetica.) LUCHERINI, T., and CASTAGNOLI, M. (1954). *Reumatismo*, **6**, 286. 6 figs, bibl.

Psychogenic Rheumatism. Some Special Diagnostic and Therapeutic Considerations. STEINBROCKER, O., and NEUSTADT, D. (1954). *Missouri Med.*, **51**, 996.

Clinical Experience with Phenylbutazone (Butazolidin). FRAIN, J. B., and MORRIS, J. E. (1954). *Canad. med. Ass. J.*, **71**, 445. 1 fig., 15 refs.

Effects of Phenylbutazone on the Histology of the Synovial Membrane in Rheumatoid Arthritis. (Effetti del fenilbutazone sulla istomorfologia della membrana sinoviale nell'artrite reumatoide.) LUCHERINI, T., and NATALE, P. (1954). *Reumatismo*, **6**, 361. 14 figs, 10 refs.

Results of Treatment with G-15,903 ("Irgapyrin") of 116 Cases of Rheumatic Disease. (Resultados do emprego do G-15.903 (Irgapyrin) em 116 portadores de afecçoes reumáticas.) HOULI, J., DIAS VELLOSO, G., and PINHEIRO MARTINS, A. (1954). *Rev. argent. Reum.*, **19**, 94. 25 refs.

Pharmacological and Clinical Properties of "G 25671", a New Preparation of the Pyrazolidin Series. (Über die pharmakologischen und klinischen Eigenschaften von G 25671 (Geigy Basel), einem neuen Präparat aus der Pyrazolidinreihe.) WILHELMI, G., and CURRIE, J. P. (1954). *Schweiz. med. Wschr.*, **8á**, 1315. 43 refs.

***d*-Amphetamine Sulphate as an Adjunct to the Treatment of Rheumatic Diseases.** BANGHART, H. E., and WARTER, P. J. (1954). *Amer. Practit. (Philad.)*, **5**, 867. 8 refs.

Disk Syndrome

Cervico-Brachial Pain. (Algias cervico braquiales.) CERDA C, M., and ZELDIS M, A. (1954). *Rev. argent. Reum.*, **19**, 153. 35 refs.

Gout

Effects of Phenylbutazone in Gout. JOHNSON, H. P., ENGLEMAN, E. P., FORSHAM, P. H., KRUPP, M. A., GREEN, T. W., and GOLDFIEN, A. (1954). *New Engl. J. Med.*, **250**, 665. 4 figs, 12 refs.

The authors report upon the use of phenylbutazone in the treatment of ten patients with acute gouty arthritis and sixteen cases of chronic gout at the Veterans Administration Hospital, San Francisco. The drug was given either by intramuscular injection in 20 per cent. aqueous solution, or by mouth in enteric-coated capsules. The daily dose in the acute cases was 0·8 to 1 g., but varied in the chronic cases from 0·4 to 1 g. Subjective relief was obtained in nineteen out of twenty attacks of acute gout, and the number of exacerbations was effectively reduced in the chronic cases. Toxic symptoms, however, occurred in nine of the sixteen cases of chronic gout. The majority of these occurred during the first few weeks of treatment, but the fact that some occurred later suggests that the drug should not be used as a routine in chronic gout unless all other forms of treatment have failed.

The exact mode of action of the drug is not known; it lowers the blood uric acid level and also diminishes urinary excretion of uric acid, 17-hydroxycorticoids, and sodium. The authors do not advocate the routine use of phenylbutazone in the treatment of gout; they merely indicate its therapeutic effect and recommend consideration of its use in cases of gout resistant to other established forms of treatment. *R. E. Tunbridge.*

Treatment of Gout with H.P.C. ROSS, D. N. (1954). *Brit. med. J.*, **2**, 782. 6 refs.

The author, from the General Hospital, Newcastle upon Tyne, describes the results obtained with 3-hydroxy-2-phenyl-4 cinchoninic acid (HPC), a derivative of cinchophen, in the treatment of ten cases of gout, and briefly records two further cases. The dosage was 1 to 2 g. daily for an initial period, usually a few days, then 0·5 to 1 g. daily.

Satisfactory results were obtained in acute gout, apparently quite as good as some obtained with colchicine. The drug was also effective in the chronic type of gouty arthritis, but in these cases more prolonged treatment was necessary. Administration of the drug had often to be interrupted, however, because of troublesome skin reactions; erythema was a frequent early reaction and vesiculation was observed later in six cases. Nevertheless, the drug was persevered with, in some cases for

long periods; one patient received a total of 210 g. HPC within a trial period of 9 months. No serious toxic effects were observed; nausea and diarrhoea, which occurred in some cases, could usually be prevented by giving the drug in small doses after the main meals with an equal amount of sodium bicarbonate. In the author's view HPC should be reserved for short-duration treatment of acute gout or for prophylactic treatment of patients with premonitory symptoms. *Joseph Parness.*

Some New Drugs in the Treatment of Gout. (Quelques nouveaux médicaments de la goutte.) FRANÇON, F., and FRANÇON, J. (1954). *Presse therm. clim.*, **91**, 171.

Treatment of Gout with Phenylbutazone. (Beitrag zur Therapie der Gicht mit Butazolidin.) HUNZIKER, H. (1954). *Z. Rheumaforsch.*, **13**, 296. 7 figs, 10 refs.

Renal Action of Benemid. (L'action rénale du Bénémid.) COURJARET, J. (1954). *Presse therm. clim.*, **91**, 174. 8 refs.

Articular Manifestations of Gout. (Les manifestations articulaires de la goutte.) VIGNON, G. (1954). *Presse therm. clim.*, **91**, 184.

Gouty Manifestations in Sites other than the Big Toe. (Accès de goutte articulaire en dehors de l'orteil.) SÉRANE, J. (1954). *Presse therm. clim.*, **91**, 161.

Spa Treatment for Sthenic Gout. (Traitement hydrominéral de la goutte sthénique.) VIOLLE, P. L. (1954). *Presse therm. clim.*, **91**, 188.

Gout and Allergy. (Goutte et allergie.) LAROCHE, C., and PAOLAGGI, J. (1954). *Presse therm. clim.*, **91**, 164. 28 refs.

General Pathology

Studies of Serum Protein Fractions in Inflammatory Rheumatism. (Études sur la répartition des protides sériques dans les rhumatismes inflammatoires. (Électrophorèse sur papier).) JACQUELINE, F., TRAVERSE, P. M. DE, and BESSON, L. (1954). *Rev. Rhum.*, **21**, 329. 41 refs.

The authors have determined at the Institutes of Hydrology and Climatology, of Paris and Aix-les-Bains, the serum protein levels in 97 cases of inflammatory rheumatism, comprising 62 cases of rheumatoid arthritis, eight of Still's disease, 24 of ankylosing spondylitis, and three of gout. The serum protein level was below normal in only eight of the cases, and was generally raised, being higher in men than in women. Except in cases of ankylosing spondylitis, in which the serum protein level was always raised, the degree of hyperproteinaemia was roughly proportional to the activity of the disease and to the erythrocyte sedimentation rate.

Paper electrophoresis of serum from patients with rheumatoid arthritis showed that the albumin fraction decreased and the globulin fraction increased as the disease became more active. Variations in the globulin fraction were found to be related to the type of arthritis. In early cases the alpha-2 globulin value was raised, whereas in more advanced cases showing fibrous or ankylosing changes, the gamma globulin value also rose. The electrophoretogram in long-standing cases showed an increase in alpha-1 globulin if the disease was active, but this value was within normal limits in quiescent cases. The beta globulin value was slightly raised in one-fifth of cases. The changes in protein fractions in cases of Still's disease were similar to those in the adult type of rheumatoid arthritis. In the cases of ankylosing spondylitis the changes in the globulin fractions were less marked, and the authors believe this was associated with the less intense activity of the disease. In two of the three cases of gout there was a rise in gamma globulin level, but in the third case there was no change even during an acute attack.

It is concluded that these findings are not specific for the diseases discussed, but may be of help in assessing prognosis and confirming the diagnosis of the type of lesion present. *F. Clifford Rose.*

Haemagglutinating Factor in Rheumatoid Arthritis. (Den hämagglutinerande faktorn vid rheumatoid arthrit.) SVARTZ, N., and SCHLOSSMANN, K. (1954). *Nord. Med.*, **51**, 668. 5 refs.

In a further investigation carried out at the Karolinska Hospital, Stockholm, of the factor present in the serum of patients with rheumatoid arthritis which agglutinates sensitized sheep erythrocytes, inactivated serum was treated with sheep cells to remove heterophile antibody, diluted with 14 vol. water, and kept at 4° C. for 48 hours; the precipitate which formed was separated by centrifugation and redissolved in saline. This solution was found to contain a haemagglutinin for sensitized sheep erythrocytes which was specific to serum from rheumatoid arthritic patients. A factor with similar properties could be produced *in vitro* by growing bacteria isolated from the throat of patients with rheumatoid arthritis on a medium containing bovine or human collagen tissue.

D. J. Bauer.

Serological Investigations in Chronic Inflammatory Rheumatism. (Recherches sérologiques dans les rhumatismes inflammatoires chroniques.) JACQUELINE, F., EYQUEM, A., and JOCHEM, E. (1954). *Rev. Rhum.*, **21**, 399. 32 refs.

The serum of patients affected by various types of chronic inflammatory rheumatism have been titrated at the Pasteur Institute, Paris, for antistreptolysin-O (by the method of Todd and Kalbak) and the results compared with those obtained in normal subjects and in patients suffering from acute articular rheumatism. Although a titre of 200 units is generally taken as the upper limit of normal in Europe, a titre between 200 and 400 units was found in 7·8 per cent. of a control series of 115 normal subjects aged 20 to 60 years, the corresponding figure given in reports from different European countries varying from 6 to 26 per cent.

Of 393 cases of rheumatoid arthritis in adults, a raised titre was found in 52·6 per cent., the titre being 800 units

or more in 11·8 per cent. The proportions of men and women with high titres were much the same, but a higher proportion of increased titres was found among patients with a history of infection of any sort preceding the onset of the disease or of an exacerbation than among those with no such history. A high titre was found less often when the erythrocyte sedimentation rate (E.S.R.) was below 20 mm./hr, and more often in patients with marked constitutional symptoms. In four out of five cases of rheumatoid arthritis in children the titre was more than 200 units. A high titre was found in 61·2 per cent. of 96 cases of ankylosing spondylitis. This proportion is similar to that found in rheumatoid arthritis, but included a greater number of cases in which the E.S.R. was normal or only slightly raised. In spondylitis, however, the E.S.R. is often not in harmony with the clinical signs of activity. A titre of between 200 and 800 units was found in fourteen out of 21 cases of chronic gouty polyarthritis, and in twelve out of nineteen cases of psoriatic rheumatism. Repeated examinations carried out on 77 of these patients over periods up to 2 years showed a variation in titre in only nineteen per cent. of cases.

The proportion of cases of acute articular rheumatism in which an increased antistreptolysin titre has been reported by previous writers has varied from 69 to 100 per cent. Among twenty such cases the present authors found seven with a titre between 200 and 800 units, and eleven with a titre above 800 units. In the absence of a large series of cases of rheumatoid arthritis in children, however, a comparison between the findings in rheumatoid arthritis and rheumatic fever cannot strictly be made.

Kenneth Stone.

Serological Differential Diagnosis of Certain Forms of Chronic Rheumatism. (Zur serologischen Differentialdiagnostik einzelner Formen des chronischen Rheumatismus.) SEIFERT, H., and TICHY, H. (1954). *Z. Rheumaforsch.*, **13**, 133. 48 refs.

In a study carried out at the Institute of Rheumatology, Dresden, the following serological tests were carried out on 228 rheumatic patients:

(1) determination of antistreptolysin titres;
(2) Rose agglutination test, using sensitized sheep erythrocytes;
(3) Paul-Bunnell test, using fresh, untreated sheep erythrocytes;
(4) Svartz and Schlossmann agglutination test, using absorbed serum and sensitized sheep cells;
(5) L-agglutination test, based on the agglutinable antigen of β-haemolytic streptococci (method of Nicholls and Stainsby).

From the results of these tests the authors conclude that high titres in Tests 2 and 5, together with low titres in Tests 1 (antistreptolysin), 3, and 4 are serologically diagnostic of rheumatoid arthritis. In cases of ankylosing spondylitis, antistreptolysin titres were particularly high and all the other tests gave low readings. It is claimed that serological tests are of practical value in rheumatoid arthritis, since by their use a diagnosis can frequently be made before the appearance of the characteristic clinical changes and of the accelerated erythrocyte sedimentation rate.

[The original paper should be consulted for the various serological techniques which are given in some detail.]

D. Preiskel.

Disposition of Intra-Articularly Injected Hydrocortisone Acetate, Hydrocortisone and Cortisone Acetate in Arthritis. I. Concentrations in Synovial Fluid and Cells. ZACCO, M., RICHARDSON, E. M., CRITTENDEN, J. O., HOLLANDER, J. L., and DOHAN, F. C. (1954). *J. clin. Endocr.*, **14**, 711. 3 figs, 6 refs.

Studies have been made in an effort to gain some understanding of the reason for the difference in anti-arthritic effect of intra-articular injections of cortisone and hydrocortisone. The results are as follows:

(1) The rates of decrease in concentration of 17-hydroxycorticoids in the joint fluid during the first few hours after intra-articular injections of hydrocortisone, hydrocortisone acetate and cortisone acetate are approximately the same, the effect of differences between some clinical subjects being greater than that of differences between compounds.
(2) The hydrolysed forms of both hydrocortisone acetate and cortisone acetate were present in greater proportions in the fluid than in the cells.
(3) The proportion of 17-hydrocycorticoids present in the cells after injection of cortisone acetate is greater than after the injection of the free form of hydrocortisone, but less than after the injection of hydrocortisone acetate.

These data do not afford an explanation for the difference in anti-arthritic effect between hydrocortisone and cortisone. Further studies are in progress.

[*Authors' summary.*]

Relationship between Muscle Damage and the Aschoff Cell in Rheumatic Carditis. RUEBNER, B. (1954). *J. Path. Bact.*, **68**, 101. 4 figs, 24 refs.

The hearts of 32 patients dying of rheumatic carditis (of which seventeen form the basis of this study) were examined at the University of Bristol in order to determine whether necrosis of muscle fibres occurs in rheumatic carditis and whether Aschoff bodies originate from damaged muscle cells or from connective-tissue cells—two questions which have been much disputed.

As a result of his study the author is led to the conclusion that the characteristic cells are not of muscular origin. He noted that there was a more intimate relationship between the Aschoff bodies and myocardial cells in cases with a brief clinical history. He concludes that the underlying lesion is a fibrinoid necrosis of the interstitial connective tissue which also involves the thin sarcolemma of the muscle fibres, and that this is sometimes accompanied by secondary damage to the muscle cells.

A. C. Lendrum.

Specific Serological Methods in the Diagnosis of Rheumatic Processes. (Métodos serológicos específicos para el diagnóstico de los procesos reumáticos.) FOZ, A. (1954). *Rev. esp. Reum.*, **5**, 412.

Changes in Complement and its Fractions in Rheumatoid Arthritis and its Relation with the Haemagglutinating Factor. (Sul comportamento del complemento e delle sue frazioni nell'artrite reumatoide e sui suoi rapporti col fattore emoagglutinante.) CASTELLI, D., and DANEO, V. (1954). *Reumatismo*, **6**, 346. 1 fig., 20 refs.

Changes in Serum Polysaccharides in Rheumatic Disease. (Comportamento dei polisaccaridi proteici nelle malattie reumatiche.) DANEO, V., and EINAUDI, G. (1954). *Reumatismo*, **6**, 316. 1 fig., 18 refs.

Blood Protein Content in the Clinical Diagnosis of Chronic Rheumatic Diseases. (Das Bluteiweissbild in der klinischen Beurteilung chronisch rheumatischer Erkrankungen.) GAMP, A., and OSWALD, H. (1954). *Z. klin. Med.*, **151**, 397. 22 refs.

Some Properties of Human and other Synovial Fluids. FESSLER, J. H., OGSTON, A. G., and STANIER, J. E. (1954). *Biochem. J.*, **58**, 656. 2 figs, 9 refs.

Experimental Researches on the Nature of the Waaler-Rose Reaction. (Ricerche sperimentali sulla natura della reazione di Waaler-Rose.) DANEO, V., and EINAUDI, G. (1954). *Reumatismo*, **6**, 356. 10 refs.

Dural Nodules in Rheumatoid Arthritis. Report of a Case. MAHER, J. A. (1954). *Arch. Path.* (*Chicago*), **58**, 354. 6 figs, 26 refs.

Influence of Long-Term Treatment with Glycuronic Acid Lactone on the Activity of Tissue Hyaluronidase. (Über den Einfluss einer langdauernden Behandlung mit Glucuronsäure-lacton auf die Aktivität der Gewebshyaluronidase.) HOLLMANN, S., and WILLE, E. (1954). *Z. Rheumaforsch*, **13**, 202. 1 fig., 14 refs.

Splenic Neutropenia in the Felty Syndrome. HUTCHISON, H. E., and ALEXANDER, W. D. (1954). *Blood*, **9**, 986. 3 figs, bibl.

ACTH, Cortisone, and Other Steroids

Experiences with ACTH and Cortisone. A Note on Long-Term Therapy. MCGEHEE, E. H., and MACLEAN, K. (1954). *Brit. med. J.*, **1**, 1171. 15 refs.

The authors' experience at Guy's Hospital, London, during a 2½-year period in the treatment of various diseases with cortisone and ACTH is briefly reviewed. Patients receiving these drugs for the first time were treated for about 3 weeks according to one of the following dosage schedules:

(1) 20 to 40 mg. ACTH daily by slow intravenous infusion for a minimum of 8 and occasionally up to 16 hrs;
(2) 20 to 40 mg. ACTH gel daily by a single intramuscular injection;
(3) 100 to 200 mg. cortisone by mouth daily in four divided doses;
(4) 100 to 150 mg. cortisone daily in a single intramuscular injection.

When it was apparent that the disease was controlled, usually in 7 to 14 days, the daily dose of cortisone was reduced or ACTH was administered on alternate days. Serum sodium and potassium levels were estimated initially, such estimation being repeated only if intensive treatment was continued for more than 2 weeks or the patients' condition required it. When the drugs were given daily, fluid intake was restricted in apyrexial patients to 50 to 60 oz. (1·4 to 1·7 l.) a day. No additional sodium chloride was permitted, but up to 4 g. potassium chloride was given daily.

The disease conditions in 185 patients are tabulated. Complications included gastro-intestinal perforation in three cases (the classic early symptoms being masked by the drugs), with two deaths; acute psychosis in three cases; and steroid diabetes in one case.

The results of long-term out-patient treatment in 44 cases are discussed. Of these 44 patients, eighteen had Addison's disease or pituitary dysfunction, three polyarteritis nodosa, two disseminated lupus erythematosis, one subacute collagen disease, five scleroderma, one rheumatoid arthritis, six pemphigus, two exfoliative psoriasis (response poor), and six eye diseases. The results were highly satisfactory; in many of the cases the disease underwent remission so that treatment could be stopped, at any rate for a time. *Norval Taylor.*

Interactions between Systemic and Local Stress. SELYE, H. (1954). *Brit. med. J.*, **1**, 1167. 1 fig., 23 refs.

Using the granuloma-pouch technique, it was shown that, depending upon circumstances, systemic stress can either inhibit or aggravate the topical damage caused by exposure of a limited tissue area to a pathogen—for example, a chemical irritant, such as croton oil.

The antiphlogistic effect of stress is not merely due to increased secretion of cortisol-like hormones, since it is also observed in adrenalectomized animals maintained on (in themselves inactive) threshold doses of injected cortisol. The aggravation of topical tissue injury by systemic stress also depends only in part upon endogenously produced adrenal hormones; it is abolished by complete adrenalectomy, but not if suitable substitution therapy with antiphlogistic corticoids (cortisone, cortisol) is given. Both these effects of systemic stress upon topical tissue reactions can be delayed, becoming manifest only after the systemic stressor has ceased to act.

The interrelation between systemic and local manifestations of disease in general are discussed in the light of these findings.—[*Author's summary.*]

Urinary Excretion of Adrenocortical Steroids by Patients receiving Salicylates. SMITH, M. J. H., GRAY, C. H., and LUNNON, J. B. (1954). *Lancet*, **1**, 1008.

It has been suggested that salicylates act in rheumatic diseases by stimulating the adrenal cortex via the anterior pituitary to produce adrenocortical steroids, which are considered to be the active therapeutic agents. Some of the evidence supporting this hypothesis and some conflicting with it is here cited.

In the present study, carried out at King's College Hospital Medical School, London, the authors investigated the urinary excretion of adrenocortical steroids in five patients receiving salicylates, a paper-chromatographic method which allows separate assay of cortisone, 17-hydroxycorticosterone, and tetrahydrocortisone being employed.

The patients investigated included three women with rheumatic fever and one woman and one man with rheumatoid arthritis. All patients received 4-hrly doses of sodium salicylate totalling 150 to 200 gr. (10 to 13 g.) daily, and the excretion of adrenocortical steroids in 24-hr specimens of urine and the plasma salicylate levels were determined.

In no case did salicylate administration affect the urinary adrenocortical steroid excretion, even when, as in one instance, the dosage of salicylate reached a toxic level. Subsequent administration of corticotrophin to two of the patients was followed by a large increase in steroid output. It is clear, therefore, that these results do not support the hypothesis that the therapeutic activity of salicylate depends on the intermediary production of corticotrophin. *Nancy Gough.*

Salicylates and the Plasma Level of Adrenal Steroids. BAYLISS, R. I. S., and STEINBECK, A. W. (1954). *Lancet*, **1**, 1010. 2 figs, 16 refs.

This paper from the Postgraduate Medical School of London reports a study of the plasma level of adrenocortical steroids during salicylate therapy which was undertaken as a direct approach to the problem of whether or not salicylates stimulate the pituitary–adrenal system. Observations were made on eleven patients with either rheumatic fever or rheumatoid arthritis. The plasma levels of 17-hydrocycorticosteroids (cortisone and hydrocortisone) were measured by the authors' modification of the method of Nelson and Samuels (*J. clin. Endocr.*, 1952, **12**, 519) and the plasma salicylate level by the method of Brodie and others. Seven of the patients received prolonged treatment with salicylates in a dosage of 0·75 to 1·75 g. 4-hrly, and four were given a single dose of 3·3 to 5·3 g., which is sufficient to raise the plasma salicylate concentration to 20 mg. or more per 100 ml.

In no case was there any significant effect on the level of circulating adrenocortical steroids. Hence the authors conclude that salicylates in clinical dosage do not stimulate the pituitary–adrenal system. They add that toxic doses of salicylate may increase the blood level of adrenocortical hormones, but this is merely the normal response to any non-specific poison. *Nancy Gough.*

Effect of ACTH on the Adrenals in the Nephrotic Syndrome and Rheumatic Fever. LANDING, B. H., and FERIOZI, D. (1954). *J. clin. Endocr.*, **14**, 1023. 2 refs.

In a study carried out at the Children's Medical Center (Harvard Medical School), Boston, the adrenal glands of three untreated patients with the nephrotic syndrome due to chronic glomerulonephritis were smaller in weight and had a higher fat content than the glands from patients with untreated rheumatic fever. Administration of ACTH (corticotrophin) to the nephrotic patients produced an increase in zone thickness and cell size in all three zones of the adrenal cortex, these values returning to normal on withdrawal of the hormone. In the patients with rheumatic fever, ACTH provoked a greater response in the zona fasciculata than in the zona reticularis. *F. W. Chattaway.*

Effect of Adrenocorticotropic Hormone and Cortisone Acetate on the Urinary and Blood Levels of Ascorbic Acid in Man. BECK, J. C., BROWNE, J. S. L., and MACKENZIE, K. R. (1954). *J. clin. Endocr.*, **14**, 1006. 10 figs, 21 refs.

At McGill University Clinic, Royal Victoria Hospital, Montreal, the authors have studied the effect of ACTH and cortisone acetate on the blood and urinary ascorbic acid levels of 32 chronically diseased patients receiving supplements of 250 or 1,000 mg. ascorbic acid, or on a normal diet containing from 15 to 90 mg. ascorbic acid per day.

Of 27 patients receiving ACTH, 21 showed an increased urinary excretion of ascorbic acid extending over the first 24 to 48 hrs of hormone administration, and a reduction of excretion on withdrawal of the hormone. Of nine patients receiving cortisone acetate intramuscularly, three showed similar changes in ascorbic acid excretion; in six cases there was no response, possibly owing to slow absorption of the cortisone, since three patients receiving cortisone by mouth all showed increased excretion of ascorbic acid. The dietary level of ascorbic acid did not appear to affect the type of response observed. Two scorbutic infants also showed increases in urinary ascorbic acid excretion after injection of ACTH, together with an increase in the urinary content of formaldehydogenic corticoids, accompanied by clinical improvement.

In general the blood levels of ascorbic acid rose along with the urinary levels. The possible sources of the increased ascorbic acid output and the endocrinological implications of the results are discussed. It is suggested that increased glomerular filtration rate, lowered tubular reabsorptive capacity, and release of ascorbic acid from the adrenal cortex may all play a part. *F. W. Chattaway.*

Effects of Hydrocortisone Acetate in Non-Articular Rheumatism. (Des effets de l'hydrocortisone-acétate dans les rhumatismes non-articulaires.) TEIXEIRA, M. A., and BARATA, M. I. (1954). *Rev. Rhum.*, **21**, 100. 23 refs.

This article from the Institute of Rheumatology, Lisbon, records the results of treatment of various soft-tissue lesions with local injections of hydrocortisone in doses of 25 to 75 mg. The lesions included bursitis, psoriasis, epicondylitis, tenosynovitis, periarthritis of the shoulder, and sciatica. More than 200 injections were made into 85 patients.

No untoward reactions were experienced, and nearly 100 per cent. of cures were reported in epicondylitis and "tendoperiostitis", with less dramatic results in the other

lesions. No beneficial effect was produced in cases of Dupuytren's contracture or psoriasis.

W. S. C. Copeman.

Compound E, Compound F, and ACTH in the Management of Idiopathic Thrombocytopenic Purpura. ZARAFONETIS, C. J. D., STEIGER, W. A., and CARY, S. K. (1954). *Amer. J. med. Sci.*, **228**, 1. 9 figs, 11 refs.

The results of treatment with Compound E (17-hydroxy-11-dehydrocorticosterone), Compound F (17-hydroxycorticosterone), and ACTH in idiopathic thrombocytopenic purpura are reported in this paper from the Temple University School of Medicine, Philadelphia. All cases in which an allergic or drug reaction appeared to be aetiologically significant were excluded. The L.E.-cell test was performed in all the eleven cases studied to exclude a diagnosis of systemic lupus erythematosus. The reaction to the Coombs test was positive in three cases, and in two there were positive reactions to repeated serological tests for syphilis. These last reactions were proved to be false by the treponemal immobilization test, and the authors emphasize the value of this test in excluding spirochaetal infection.

As a result of treatment, haemorrhage was arrested in all cases; this was associated with an increase in capillary resistance. However, there was not always a comparable remission in the thrombocytopenia. In three cases in which the rise in the platelet count was negligible, splenectomy was performed, with apparent cure in one, a partial improvement in one, and temporary improvement only in one. In a further case an increase in the platelet count was observed at first, but this was not maintained even during treatment. In the remaining seven cases there was adequate haematological remission. The authors consider that two of these seven patients were cured after one course of steroid; the condition of two others was satisfactory at the time of the report. In three cases the platelet count increased with each course of treatment but gradually fell thereafter.

There did not appear to be any difference between the response to oral administration of Compound E or Compound F, and of ACTH, but in one case Compound F given parenterally was ineffective although there was a response when the drug was later given by mouth.

Nigel Compston.

Corticotropic Activity of Human Blood. PARIS, J., UPSON, M., SPRAGUE, R. G., SALASSA, R. M., and ALBERT, A. (1954). *J. clin. Endocr.*, **14**, 597. 28 refs.

The authors present a concise review of the present position in regard to assays for corticotrophin in human blood, and discuss the merits and demerits of various techniques that have been developed, particularly at the Mayo Laboratories, Rochester, Minn., since the earlier report by Taylor and others (*Endocrinology*, 1949, **45**, 335; *Abstracts of World Medicine*, 1950, **7**, 294).

They consider that the method of Sayers and others (*Endocrinology*, 1948, **42**, 379), which depends on the measurement of adrenal ascorbic-acid depletion in hypophysectomized rats, is still on the whole the most reliable, though in their experience it has some limitations: for example, the assay rat must be completely hypophysectomized, and the method cannot be depended on for quantitative measurement of ACTH activity, the results obtained having tended to be capricious. Another reliable method, although it requires comparatively larger amounts of blood, is that employed by Sydnor and Sayers (*Proc. Soc. exp. Biol. (N.Y.)*, 1952, **79**, 432) who used extracts of blood prepared by the oxycellulose process of Astwood and colleagues. By both these methods corticotrophic activity has been demonstrated in Addison's disease, the adrenogenital syndrome and in a few miscellaneous conditions, whereas no activity could be detected in normal persons or in patients with Cushing's disease or febrile miliary tuberculosis. A number of other workers have claimed to have found high corticotrophic activity in normal serum, but their results have so far been too contradictory to be relied on.

Richard de Alarcón.

Adrenocortical Function and Metabolism of 17-Hydroxycorticosteroids in Pernicious Anemia. SANDBERG, A. A., EIK-NES, K., NELSON, D. H., PALMER, J. G., CARTWRIGHT, G. E., and WINTROBE, M. M. (1954). *New Engl. J. Med.*, **251**, 169. 7 figs, 8 refs.

The authors have conducted experiments at the University of Utah College of Medicine, Salt Lake City, to examine the claim of Strauss and Brokaw (*New Engl. J. Med.*, 1951, **245**, 798) that there is "functional adrenocortical insufficiency" in certain cases of pernicious anaemia in relapse.

Estimation of the plasma 17-hydroxycorticosteroid level in 8 cases of pernicious anaemia revealed normal values in all but one patient who was critically ill. After the oral administration of adrenal steroids (ACTH or hydrocortisone) there was a more rapid and sustained rise in the plasma level of 17-hydroxycorticosteroids than normal, but after intravenous injection the "clearance" of these steroids was unimpaired. The plasma level of 17-hydroxycorticosteroids rose normally in patients with pernicious anaemia after giving ACTH. In one patient with gastric achylia but without pernicious anaemia the level of 17-hydroxycorticosteroids was similar to that found in the plasma in cases of pernicious anaemia after the administration of adrenal corticoids by mouth. In patients with pernicious anaemia the administration of gastric juice along with adrenal steroids produced levels nearer to the normal.

The authors therefore conclude that there is no evidence of adrenal insufficiency accompanying pernicious anaemia, but that the changes they observed following the oral administration of adrenal corticoids to achylic patients were probably due to the absence of gastric juice, since normally a large fraction of the dose of corticosteroids is destroyed in the gastrointestinal tract before absorption can take place. *Nigel Compston.*

Some Observations on the Treatment of Ulcerative Colitis with ACTH. DICK, A. P., and BECKETT, A. G. (1954). *Brit. med. J.*, **2**, 378. 19 refs.

After reviewing the literature on the treatment of ulcerative colitis with cortisone or ACTH and on the

complications encountered, the authors report an uncontrolled therapeutic trial of ACTH in fourteen cases of this condition seen at Addenbrooke's Hospital, Cambridge. The hormone was given initially in a dosage of 15 mg. 6-hrly by intramuscular injection or 20 mg. daily in the form of a gel, this dosage being gradually increased until improvement, as judged by gain in weight and fall in temperature, was observed. The maximum effective dosage was continued for 2 to 5 weeks, and then gradually reduced. Details of the results and the duration of the follow-up are given in a comprehensive table, and certain cases are discussed.

In seven of the fourteen cases there was complete remission and in four some maintained improvement. The authors conclude that ACTH has a place in the management of cases of ulcerative colitis, particularly in acute and severe cases of recent onset. *J. Naish.*

Cortisone in Ulcerative Colitis. Preliminary Report on a Therapeutic Trial. TRUELOVE, S. C., and WITTS, L. J. (1954). *Brit. med. J.*, **2**, 375. 2 figs, 12 refs.

A "blind" therapeutic trial of cortisone in ulcerative colitis was carried out at the Radcliffe Infirmary, Oxford, in conjunction with similar trials at hospitals in North-west London, Edinburgh, Leeds, and Birmingham, a total of 213 patients being treated. The dosage of cortisone was 100 mg. a day for the first 3 weeks, followed by smaller doses in the next 3 weeks. Approximately half of the patients received a placebo, but the physician in charge did not know whether the patient was receiving this or cortisone.

The results obtained in first attacks and in relapses are considered separately, the patient's condition being assessed as "clinical remission", "improved", and "no change or worse". At the end of 6 weeks, in the series as a whole significantly more treated patients than controls were in clinical remission. Of the patients given cortisone during a first attack, 42 per cent. were in remission, 36 per cent. were improved, and only 22 per cent. showed no change or were worse. Of the patients given cortisone during second or subsequent attacks, the percentage in remission was slightly lower and the percentage improved was substantially lower than was the case in the patients treated during a first attack. The number of patients subjected to ileostomy and the number of deaths were higher in the controls than in the treated group. *X*-ray examination and sigmoidiscopy were not carried out in all cases, but such data as were available confirmed the general clinical assessment. A few patients had a relapse soon after cessation of cortisone therapy.

It is concluded that cortisone is beneficial in the treatment of an acute attack of ulcerative colitis.

J. Naish.

Treatment of Dermatoses with Local Application of Hydrocortisone Acetate. ROBINSON, H. M., and ROBINSON, R. C. V. (1954). *J. Amer. med. Ass.*, **155**, 1213. 5 refs.

At the University of Maryland School of Medicine, Baltimore, local application of hydrocortisone acetate in the form of a lotion or ointment in a strength of 0·5 per cent., 1 per cent., and 2·5 per cent. was tried in the treatment of 418 patients suffering from a variety of dermatoses. It was found that in a strength of 0·5 per cent. both lotion and ointment were relatively ineffective, and that in general an oily base was the most suitable vehicle. Hydrocortisone was of value in atopic dermatitis, neurodermatitis, seborrhoeic dermatitis, contact dermatitis, pruritus ani, and pruritus vulvae, but was ineffective in alopecia areata, psoriasis, pityriasis rosea, acne vulgaris, lupus erythematosus, and lichen planus. In patients with acne vulgaris the condition became worse (probably as a result of direct hormonal effect), but other untoward reactions in the series were due to sensitivity to the vehicle. In patients with chronic dermatoses there was a tendency to relapse when the hydrocortisone was discontinued; nevertheless, it is considered that the drug has an important place in the treatment of skin conditions. *H. R. Vickers.*

Treatment of Pellagra with Corticotrophin (ACTH). (Notre expérience du traitement de la pellagre par l'hormone hypophysaire corticotrope (A.C.T.H.).) MIOWSKI, D. K., and TADZER, I. S. (1954). *Ann. Derm. Syph.* (*Paris*), **81**, 259. 4 figs, 23 refs.

A clinical and laboratory investigation of fifteen cases of severe pellagra at the Dermatological Clinic of the University of Skopje, Yugoslavia, suggested a relationship between the manifestations of the disease and adrenal dysfunction. Five severe cases were therefore treated with injections of 25 mg. ACTH (corticotrophin) daily for 16 to 20 days without any other medication or change of diet. Improvement in the mental state, the condition of the skin, and the gastrointestinal symptoms was manifest in every case after six doses, and after ten doses the patients were normal in every respect except for some residual skin lesions. After 400 to 500 mg. ACTH had been given the patients were discharged cured, the only remaining sign of the disease being slight depigmentation of the skin in the areas which had been most severely affected. *James Marshall.*

Cortisone in the Treatment of Pulmonary Tuberculosis. COCHRAN, J. B. (1954). *Edinb. med. J.*, **61**, 238. 17 refs.

An interim report is presented from Dumfries and Galloway Sanatorium on the results of administration of cortisone to nine patients (six males, average age 45, and three females, average age 33) with pulmonary tuberculosis who had previously received streptomycin with PAS and/or isoniazid, the choice as regards the last two drugs depending on individual drug resistance, if any. All the patients had a positive sputum and moderate or advanced disease, four having bilateral lesions with cavitation. Streptomycin with PAS and/or isoniazid was known to be relatively ineffective in at least two of the patients.

Cortisone was given cautiously, the first patient receiving 12·5 mg., the second and third 25 mg., and the others 50 to 100 mg. daily, for 2 months. The other

chemotherapeutic drugs were given at the same time and were continued for at least another 2 months after administration of cortisone ceased.

In all the patients there was initial symptomatic improvement, which was maintained in most of them. One patient died (the influence of cortisone in this case was uncertain); in the others an increase in weight, diminished cough, and an improvement in general condition and well-being were observed. A fall in the erythrocyte sedimentation rate was noted in seventeen patients, but in most of them the rate promptly returned to the original level when cortisone was withdrawn. In four patients the radiological improvement was greater than could be expected from standard chemotherapy. With the possible exception of the fatal case, no adverse results of any consequence attributable to cortisone were observed. The author considers that the results warrant an extended trial of this form of treatment. The cases are reported in detail.

[The author's conclusion seems justified.]

R. J. Matthews.

Cortisone in Tuberculous Meningitis. (Cortisone nella meningite tubercolare.) PROSPERI, P., and ROSSI, R. (1954). *Riv. Clin. pediat.*, **53**, 413. 29 refs.

In the hope that it might improve the distribution of streptomycin in the cerebrospinal fluid (C.S.F.) in cases of tuberculous meningitis with signs of intrathecal block, the authors used cortisone in the treatment of thirty such cases in patients varying in age from 1½ to 41 years at the paediatric and other clinics of the University of Florence. Five of the patients were suffering from optic atrophy, and cortisone was given in the hope of improving the vision of these patients. The remaining 25 patients showed evidence of obstruction to the flow of C.S.F. The authors emphasize that treatment was begun at varying times in the course of the disease and that different doses of the drug were given for varying lengths of time. They cannot therefore make an accurate assessment of the results.

Of the first five cases mentioned above, there was slight visual improvement in three and none in two. Of the other 25 patients, eight received cortisone or hydrocortisone by mouth only. In two of these cases the treatment was started fairly soon after signs of blockage appeared and resulted in a great improvement in the flow of fluid. In the other six cases cortisone was given at a much later stage and little benefit resulted. The remaining seventeen patients received cortisone both by mouth and intrathecally. There was no improvement in five cases and the results were only mediocre in two, but a "good" result was obtained in two others and a "very good" result in eight. The earliest day of the disease on which cortisone therapy was started in this group was the 38th, while even in one case first treated on the 263rd day some improvement still occurred.

The authors consider that in sixteen of the 25 cases there was evidence that the block was relieved as a result of cortisone therapy, and on these grounds they are convinced of its value. *J. G. Jamieson.*

Effect of Aldosterone (Electrocortin), a New Adrenal Hormone, in Addison's Disease. (L'effet d'une nouvelle hormone surrénale, l'aldostérone (électrocortine) dans la maladie d'Addison.) MACH, R. S., and FABRE, J. (1954). *Bull. Soc. méd. Hôp. Paris*, **70**, 353. 3 figs, 7 refs.

The authors report from the University Medical Clinic, Geneva, a study of the action of the new corticoid, aldosterone, in two cases of Addison's disease. Both patients also received deoxycortone acetate under similar conditions, and the clinical and metabolic effects were compared.

One hour after the injection of aldosterone the symptoms of adrenal insufficiency had disappeared completely, this beneficial effect lasting for 6 or 7 hours. After a few days of treatment the pigmentation of the skin cleared in a striking and unexpected way. In one case, treatment with aldosterone for 6 days had more effect on the pigmentation than several months' treatment with cortisone. The changes in the electrolyte balance were similar to those obtained with deoxycortone acetate, that is, there was retention of sodium and chloride and increased potassium excretion, without, however, affecting the water balance or producing a pathological retention of water. The corticoid had no effect on the blood pressure, although haemodilution tests showed an increase in blood volume. The typical flattened glucose tolerance curve seen in adrenal insufficiency, with a marked secondary hypoglycaemia, reverted to normal after administration of aldosterone, but this effect on carbohydrate metabolism was not obtained with deoxycortone acetate.

Aldosterone is an extremely active hormone, and the authors found the effective dose in Addison's disease to be about 2·5 to 3·3 μg. per kg. body weight. It is thus some twenty to thirty times more active than deoxycortone acetate. Its action in Addison's disease is similar to that of cortisone in so far as it acts on the pigmentation and carbohydrate metabolism, but it has no effect on the leucocytes, particularly eosinophils, nor on nitrogen and water metabolism. *Richard de Alarcón.*

Combination of ACTH–Cortisone–Hydrocortisone with Antibiotics in the Management of Overwhelmingly Severe Infections. Theory and Practice based on Three Years' Experience. JAHN, J. P., BOLING, L., MEAGHER, T. R., PETERSON, H. H., THOMAS, G., FISHER, B. M., THILL, A. E., LEOVY, W. A., BALCH, H. E., and KINSELL, L. W. (1954). *J. Pediat.*, **44**, 640. 5 figs, 26 refs.

The authors here summarize their experience during the period 1950-53 in 83 cases of overwhelmingly severe infection which were considered likely to prove fatal if treated by "standard" methods, and which were treated with corticotrophin (ACTH), cortisone, or hydrocortisone in addition to antibiotics. A short, intensive course of hormone treatment was given, only the most severely ill patients receiving it for as long as 7 days. Antibiotic therapy was always continued for at least 3 days after the discontinuance of hormone administration. The conditions treated included meningococcal

infection (fourteen cases), pneumonia (six cases), peritonitis (twenty cases), and miscellaneous infections such as tetanus, diphtheritic myocarditis, hepatitis, botulism, poliomyelitis, and post-infectious encephalomyelitis.

It is argued that the effect of the hormones in reducing inflammation will in many cases prevent irreversible damage to the infected tissues and even (as in mumps orchitis) the complete destruction of an organ. The concomitant danger of dissemination of the infection is minimized by giving the hormones for only a limited period and by adequate antibiotic therapy.

Of the 83 patients treated, only 29 died, and the authors are convinced that the hormones were responsible for rapid and striking clinical improvement in the majority of cases. They advocate that as a general rule the use of ACTH and cortisone with antibiotics should be restricted to those non-surgical conditions which do not appear to be responding (or likely to respond) to antibiotic treatment alone, and to surgical conditions in which operative treatment is intended in the immediate future. They make an exception to this rule in the case of meningococcal meningitis, advocating hormonal therapy in every case. They also advocate the combined treatment in cases of acute hepatitis and mumps orchitis, despite the lack of effect of antibiotics on the viruses concerned. *R. S. Illingworth.*

Effect of Cortisone on Therapeutic Efficacy of Antibiotics in Experimental Infections. JAWETZ, E. (1954). *Arch. intern. Med.*, **93**, 850. 4 figs, 27 refs.

In a series of experiments carried out at the University of California School of Medicine, San Francisco, it was found that in two subacute bacterial infections induced in mice very small amounts of cortisone markedly interfered with the therapeutic efficacy of antibiotics. The organisms employed were *Klebsiella pneumoniae* and *Streptococcus pyogenes*, and the antibiotics were crystalline preparations of potassium benzylpenicillin, streptomycin sulphate, and chlortetracycline hydrochloride. The usual dose of cortisone was 0·75 mg. in 5 days (approximately 8 to 10 mg./kg. body weight per day); the total dose never exceeded 1 mg.

Cortisone in well-tolerated amounts lessened the therapeutic efficacy of antibiotics in lethal and sublethal infections in mice, this phenomenon being observed not only when the animals were given cortisone before infection, but also when administration of both cortisone and antibiotic was started several hours after infection. The effect varied with the size of the inoculum and the total dose of the antibiotic; it was greatest when the antimicrobial therapy was subcurative; when the dose of antibiotic was well in excess of the curative dose the reduction of its therapeutic efficacy by cortisone was no longer evident.

Cortisone interfered much more with the action of the predominantly bacteriostatic chlortetracycline than with the action of the bactericidal penicillin or streptomycin. This suggests that the effect of cortisone is mediated through host-defence mechanisms, and that bactericidal antibiotics in curative doses do not depend to so great an extent on host mechanisms and are thus less influenced by cortisone.

Cortisone in concentrations up to 2 mg./ml. had no direct effect on micro-organisms or antimicrobial drugs *in vitro*. Moreover, the drug was without effect on the total leucocyte count, the morphological differences in the tissue response to infection, and the viable bacterial counts in the tissues of experimental or control animals. The precise site and mechanism of action of cortisone are therefore undetermined. *A. W. H. Foxell.*

Experimental Study of the Stimulant Effect of Radiotherapy on the Adrenal Cortex. (Étude expérimentale de la radiothérapie stimulante des corticosurrénales.) THOYER-ROZAT, —., LAFARGUE, J., GILBERT-DREYFUS, —., SCHILLER, J., and TYAN, E. A. (1954). *J. Radiol. Électrol.*, **35**, 169. 6 figs.

In this study carried out at the Hôpital de la Charité, Paris, the adrenal areas of 96 rats were subjected to *x* irradiation at 130 kV, H.V.L. 7·4 mm. Al, through a 6-cm. layer of rice to correspond to the lumbar tissue in man (giving about 24 per cent. transmission), doses of 25, 50, or 75 r being delivered at the upper surface of the rice. The effects were assessed by changes in the weight of the glands, of the blood sugar level, and the urinary nitrogen excretion, the last two being known to be controlled by 11-oxysteroids.

The results showed that gland weight was increased, even after as short a period of irradiation as 45 minutes, increases in gland weight of up to 107 per cent. being found, as compared with controls. Blood sugar levels showed an early rise, which was maximal in about one week. Urinary nitrogen excretion was also increased for about 18 days, as compared with no significant increase in adrenalectomized controls. A dose of 75 r seemed to give the maximum effect possible. The main effects are attributed to the action on the cortex, since (*a*) stimulation of the medulla results in only a short period of hyperglycaemia followed by a later glycosuria, whereas the glycosuria in these experiments appeared before the maximal hyperglycaemia; and (*b*) similar findings to the above were obtained with ACTH and cortisone. The mechanism is thought to be by inhibition of utilization of glucose by 11-oxysteroids, accompanied by secondary gluconeogenesis, as shown by the increased nitrogen excretion.

In further experiments on five human subjects in which 100 r was delivered to the adrenal areas, increased excretion of urinary 17-ketosteroids occurred, which was maximal in 3 to 4 days. *J. Walter.*

Action of Hydrocortisone on Cells in Tissue Culture. GROSFIELD, H., and RAGAN, C. (1954). *Proc. Soc. exp. Biol. (N. Y.)*, **86**, 63. 4 figs, 11 refs.

The authors describe experiments carried out at the Presbyterian Hospital and Columbia University, New York, which confirmed that hydrocortisone when added in a concentration of 200 μg./ml. to chick embryo tissue cultures in a medium composed of chicken plasma and amniotic fluid consistently inhibited the growth of fibroblasts. This effect could be partially antagonized by the addition of embryonic extract. The growth of gastric and intestinal epithelium was not inhibited by

hydrocortisone. In heart-tissue cultures the fibroblasts whose growth had been inhibited, grew normally when the hydrocortisone was removed. Aqueous soluble deoxycortone produced similar effects to those of hydrocortisone. Minimal inhibition of growth was also seen when cholesterol in suspension was added.

Similarities and differences between these findings and those usually seen *in vivo* are indicated and discussed. The cause of the inhibitory action of embryonic extract is not clear. *Norval Taylor.*

Cortisone and Calcium Balance (Effect of Calcium, Vitamin-D, and Methylandrostenediol). [In English.] FISCHER, F., and HASTRUP, B. (1954). *Acta endocr.* (*Kbh.*), **16**, 141. 1 fig., 20 refs.

At the Rigshospital, Copenhagen, the authors have studied the effect of calcium, vitamin D, and methylandrostenediol on the calcium metabolism of a man aged 24 who was bedridden with severe spondylitis ankylopoietica and calcification of the spinal ligaments. The patient was maintained on a low-calcium diet containing 160 mg. calcium daily. Vitamin D (5,000 I.U.), cortisone, methylandrostenediol, and extra calcium were administered in varying combinations and amounts for periods of 2 to 3 weeks at a time.

On this low calcium intake the negative calcium balance was further depressed by cortisone. When the intake of calcium was raised by giving calcium phosphate and vitamin D, however, the calcium balance became positive in spite of the continued administration of cortisone; calcium retention was still further increased during a 21-day period during which methylandrostenediol was given, excretion of calcium in both the urine and faeces being reduced by the hormone. It is therefore suggested that to counteract the danger of osteoporosis in patients with Cushing's syndrome or those receiving prolonged treatment with ACTH or cortisone, calcium and vitamin D should be given freely, with, in addition, occasional short courses of methylandrostenediol. *C. L. Cope.*

A Chloro-Derivative of Cortisone with Enhanced Activity. CALLOW, R. K., LLOYD, J., and LONG, D. A. (1954). *Lancet*, **2**, 20. 7 refs.

At the National Institute for Medical Research, London, the biological activity of the compound 9α-chloro-17α-hydroxycorticosterone (9α-chloro-hydrocortisone) acetate was compared in several tests with that of cortisone acetate and hydrocortisone acetate. In a toxicity test on adult mice, in which each steroid was injected daily in doses of 50 mg./kg. body weight for 10 days, the chloro-steroid killed seven of ten mice and cortisone acetate killed three of ten mice. Atrophy of the thymus, spleen, and adrenal cortex was maximal in both groups so that the activity of the steroids could not be compared by this method. Both steroids in doses of 2·5 and 1·25 mg./kg. inhibited the growth of nestling rats to comparable degree but the chloro-steroid proved to be 3·4 times more active than cortisone acetate in causing atrophy of the thymus and 4·76 times more active in causing hypertrophy of the liver. Comparison between the chlorosteroid and hydrocortisone acetate showed that chlorine substitution increased the thymus-involuting activity of the latter 1·42 times. The chloro-steroid was about 5 times more effective than cortisone acetate in depressing sensitivity to tuberculin in guinea-pigs infected with B.C.G. *C. L. Cope.*

A Long-Acting Ester of Cortisone. (Über einen langwirkenden Cortisonester.) DESAULLES, P., and MEIER, R. (1954). *Schweiz. med. Wschr.*, **84**, 741. 2 figs, 10 refs.

For the purposes of a search for derivatives of cortisone with prolonged action when given parenterally, routine tests were adopted which permitted both the therapeutic effect and the general effects of the substance under consideration to be gauged. Of the latter the effect on the body weight and the weight of the adrenal glands appeared to be of most importance, while a modification of the "granuloma test" was used to determine the therapeutic effect. These tests permit the assessment not only of the duration of action of the substance, but also of its intensity.

The procedure employed was as follows. Male rats of 100 to 110 g. were given a single injection of 150 mg. of the substance to be investigated per kg. body weight. On the day of the injection and on the 2nd, 4th, 8th, and 16th days thereafter, a group of rats were anaesthetized and pressed raw cotton wool pads were implanted bilaterally in the back, the animals being killed and a *post-mortem* examination carried out after a further 7 days. The granulomata thus produced were weighed when fresh and in a dry condition, as were also the adrenal glands.

With all compounds tested the loss of weight of the granulomata in treated animals was significantly greater than in control animals. Cortisone acetate exerted its maximum effect on granulomata induced on the day of injection, and the weight of granulomata induced on the 4th day was only slightly less than in the controls. The effect of cortisone trimethylacetate was also noticeable on granulomata induced on the day of injection, but the maximum effect was on those induced on the 2nd day, when the effect of cortisone acetate was already waning, while its effect on granulomata induced 16 days after the injection was equal to that of cortisone acetate 4 days after injection. A similar difference was evident on comparing the increase of body weight and the weight of the adrenal glands in animals treated with these two preparations. Besides permitting assessment of the length and intensity of action of the test substances, the experiment also confirms that at a given intensity and duration of the effect there is only one crystal form of the seroid hormone ester which will guarantee the optimum action without side-effects. *V. C. Medvei.*

Apparent Exophthalmos in the Rat following Cortisone Treatment or Thyroidectomy. BOAS, N. F., and SCOW, R. O. (1954). *Endocrinology*, **55**, 148. 3 tables, 3 figs.

Exophthalmos in rats following cortisone treatment or thyroidectomy has been recently reported. As such

treatment retards growth generally and the exophthalmos is found only in young retarded animals, such experiments were repeated and the eyes and orbital contents weighed after apparent exophthalmos had appeared. The results clearly show that the weight of the orbital contents actually decreased in the operated animals and that the exophthalmos was only an indication of the normal growth rate of the eyeball in the presence of marked inhibition of head and body growth.

E. S. Perkins.

Hyperpyretic Basedow's Disease in a Child: ACTH Treatment. (Maladie de Basedow juvénile à forme hyperpyrétique, guérie par l'A.C.T.H.) CHARLEUX, G., LACROSAZ, and DOMBRE (1953). *Pediatrie*, **8**, 945.

An interesting case report of Basedow's disease with slight exophthalmos in a 14-year-old girl. An acute hyperpyretic episode with rheumatism and an increase of the goitre and exophthalmos responded within a few days to ACTH injections. *S. Vallon.*

Maintenance Cortisone in Intractable Asthma. Preliminary Observations of Undesirable Cortisone Effects. IRWIN, J. W., HENNEMAN, P. H., WANG, D. M. K., and BURRAGE, W. S. (1954). *J. Allergy*, **25**, 201. 4 figs, 4 refs.

In 23 cases of perennial severe asthma of undetermined aetiology seen at Massachusetts General Hospital, the symptoms were brought under control by the parenteral or oral administration of cortisone in high doses. Then the dosage was gradually decreased until symptoms reappeared, so enabling a maintenance dose to be established at a slightly higher level. In twelve of these patients the maintenance dose was 62·5 or 75 mg., while in the others it varied between 50 and 150 mg.

In this way many of these patients have been maintained without symptoms for 3 years. All of them developed some minor side-effects such as "moon face", facial hair, or acne, and all but one gained weight, some of them considerably, but diabetes, oedema, hypertension, and potassium deficiency did not occur. One patient developed marked hypercalcuria and showed evidence of osteoporosis, calcium output falling to normal when cortisone was stopped and rising again when it was resumed. In five other cases a high urinary calcium content was repeatedly found, but there was no evidence of osteoporosis. *H. Herxheimer.*

Hydrocortisone Treatment of Pollinosis. Preliminary Report. TRAYNOR, M. V., HENDERSON, L. L., PRICKMAN, L. E., KOELSCHE, G. A., CARRYER, H. M., and PETERS, G. A. (1954). *Ann. Allergy*, **12**, 263. 2 refs.

Hydrocortisone was given by mouth at the Mayo Clinic to thirteen patients suffering from ragweed hayfever (seven of whom also had asthma) who had not benefited from desensitization. The daily dose varied initially from 30 to 160 mg., average 80 mg., and after a few days this was reduced to 30 to 40 mg. The duration of the course varied from 2 to 14 days. All the patients benefited from the treatment, the relief obtained being described as either "good" or "excellent". In some cases the relief lasted for the remainder of the pollen season although treatment was discontinued and the pollen count remained high. This symptomatic treatment is, in the opinion of the authors, justified only in certain carefully selected cases. *H. Herxheimer.*

Endarteritis Diffusa; an Allergic Manifestation. (Endarteritis diffusa; en allergisk manifestation.) HENRIKSEN, E. (1954). *Ugeskr. Læg.*, **116**, 792. 3 figs, 14 refs.

The author describes a case of diffuse endarteritis, seen at the Frederiksberg Hospital, Copenhagen. The patient was a 69-year-old diabetic woman, in whom the diabetes was satisfactorily controlled by insulin. Two days after the completion of a 4-day course of benzylpenicillin—administered for an indefinite illness manifested by general weakness, nausea, and pain in the chest—she developed pain in both hands, which was followed by oedema and cyanosis. Eventually gangrene of several finger-tips developed, leading to loss of one distal phalanx. Petechial haemorrhages, epistaxis, haematuria, and deterioration of a previously noted diabetic retinopathy completed the picture. Skin biopsy showed obliteration or narrowing of the smaller vessels and degeneration of the endothelium.

The patient was treated with ACTH, 60 mg. daily in divided doses being given initially and then in gradually diminishing doses, for 20 days. A course of di-penicillin for hypostatic pneumonia led to no complications, but a further course given for suppuration in a gangrenous finger caused pruritus, sneezing, and conjunctival inflammation. The progress of the endarteritis was arrested, however, and the diabetes, control of which had become unbalanced during ACTH therapy, returned to its former state. *H. F. Reichenfeld.*

Prolonged Therapy with Cortisone for Chronic Skin Diseases. SULZBERGER, M. B., and WITTEN, V. H. (1954). *J. Amer. med. Ass.*, **155**, 954. 2 figs, 7 refs.

The dermatological indications for cortisone therapy can be divided broadly into two groups:

(1) as a short-term measure in certain acute but ordinarily self-limited eruptions, such as widespread eczematous dermatitis, acute urticaria, angioneurotic oedema, and certain drug reactions;

(2) for long-term use in:
  (*a*) certain chronic, not ordinarily fatal, but severely incapacitating dermatoses, such as atopic dermatitis, exfoliative erythrodermia, or exudative discoid and lichenoid chronic dermatosis,
  (*b*) ordinarily fatal but chronic conditions such as pemphigus and acute disseminated lupus erythematosus.

When cortisone has to be given daily in doses of 75 mg. or more for months or even years special problems arise and the authors discuss these on the basis of some 4 years' experience. They first emphasize the need before treatment to exclude the presence or history of cardiac, renal or pulmonary disease, gastric or duodenal ulcer, tuberculosis, diabetes, thrombo-embolic diseases, and psychiatric disturbances. This is always desirable even when

short-term administration only is contemplated, and is imperative whenever a patient is expected to have to take cortisone for a prolonged period.

The results of the treatment with cortisone of 35 patients with a variety of dermatoses (including fifteen cases of atopic dermatitis) for periods ranging from 2 months to several years are given in tabular form, and were almost universally good. The initial dosage varied from 300 to 1,000 mg. daily in the "fatal" conditions, whereas many of the non-fatal skin diseases could be brought under control by doses of 100 to 300 mg. a day. Otherwise healthy persons were given an initial dosage sufficiently large to allay the signs and symptoms rapidly, the dosage then being reduced as rapidly as possible to the lowest effective maintenance level. In general it was found inadvisable to attempt to relieve the signs and symptoms completely, adverse effects being better avoided by giving doses just short of the amount required to achieve this. Such adverse reactions rarely occurred except when doses of more than 100 to 125 mg. were given daily for a protracted period. As precautionary measures the blood pressure and weight were recorded frequently, the urine tested for sugar, and a salt-poor diet given together with a daily supplement of 3 g. potassium chloride in several doses.

The authors stress the need for the regular and frequent supervision of ambulatory patients and emphasize that cortisone may mask the signs of active infection, render painless the perforation of a viscus, reduce fever, and maintain a feeling of well-being in the face of serious infection and destruction of tissue. The most encouraging experience in the prolonged administration of cortisone was that in almost all cases the dosage could be reduced, often to a fraction of that originally required, and in a few cases discontinued altogether without a recurrence of the disease. There were no instances of acquired drug resistance or of addiction.

E. E. Prosser Thomas.

Treatment of Chronic Joint Diseases with Cortisone and ACTH on the Basis of Personal Experience. (Léčeni chronických chorob kloubnich cortisonem a adrenokortikotropnim hormonem na podkladě vlastnich zkušenosti.) LENOCH, F., and KNOBOVÁ, J. (1954). *Čas. Lék. čes.*, **93**, 1121. 7 figs, 21 refs.

Cortisone in the Rehabilitation of the Arthritic Patient. BRODKIN, H. A. (1954). *J. med. Soc. N.J.*, **51**, 411.

Psychical Disturbances due to Cortisone and ACTH. (Psychische Störungen durch Cortison und ACTH.) WYSS, S. (1954). *Z. Rheumaforsch.*, **13**, 195. 12 refs.

Excretion of β-17-Ketosteroids in Polyarthritis after Infusion of ACTH. (Zur Ausscheidung von β-17-Ketosteroiden bei Polyarthritis nach ACTH-Infusionen.) ENZINGER, J. (1954). *Wien. Z. inn. Med.*, 35, 390. 4 figs, 7 refs.

Temporal Arteritis "cured" by Cortisone. (Un cas d'artérite temporale "guéri" par la cortisone.) SÈZE, S. DE, and DENIS, A. (1953). *Rev. Rhum.*, **20**, 233.

Use of ACTH Gel in Infective Joint Conditions. (Esquema personal de utilización del A.C.T.H.-gel en los procesos articulares infecciosos.) COSTA BERTANI, G. (1954). *Rev. argent. Reum.*, **19**, 126. 4 refs.

Other General Subjects

Raynaud's Phenomenon due to Vibrating Tools. Neurological Observations. MARSHALL, J., POOLE, E. W., and REYNARD, W. A. (1954). *Lancet*, **1**, 1151. 2 figs, 13 refs.

The authors report from the Oxford United Hospitals a clinical survey of 37 men suffering from Raynaud's phenomenon, the diagnosis of which was made on the history alone. The condition was found to be present in 29 out of 31 men using a pneumatic hammer delivering 2,300 blows per minute, and in eight out of 9 men using a trip hammer [the frequency of which is not stated]. Sensory loss in the affected fingers was estimated by:

(*a*) the assessment of the sense of light touch made with graded nylon threads and by the response to pinprick, using a standard needle variously weighted;

(*b*) from the time of onset of numbness due to ischaemia after application of a sphygmomanometer cuff.

In addition, four men were examined by means of a nerve clamp which rendered a segment of the ulnar nerve in the upper arm ischaemic.

There are two views of the causation of Raynaud's phenomenon, one being that it is due to a local fault in the condition of the digital arteries, the other that overactivity of the vasomotor nerves is the primary cause. From the fact that in the cases examined a permanent sensory deficit was common in association with Raynaud's phenomenon, the present authors conclude that lesions in the peripheral nerves are the probable cause. Motor weakness was also elicited in the abductor digit minimi in ten cases, in the first dorsal interosseous muscle in four cases, and in the long flexors of the fingers in four cases. Owing to the nature of the job, the left hand only was affected in the majority of the men using the pneumatic hammer, the condition starting in the terminal phalanx of the little finger; in the men using the trip-hammer both hands were affected. The condition caused little disability and the use of the pneumatic hammer was not a precipitating factor, for if an attack was present it soon passed off when the men started work. Attacks were not particularly related to cold, many of the men developing attacks when their hands were warm. The condition commonly developed from 3 months to 2 years after starting this type of work and was not cured by removing the men from it. From their experimental observations the authors conclude that there are disturbances in the peripheral nerves and that these may be the main cause of the simultaneous blanching of the fingers and the motor and sensory changes.

[The incidence of Raynaud's phenomenon observed at this factory appears to be much higher than that recorded by other workers.] *L. G. Norman.*

Raynaud's Phenomenon in Workers with Vibratory Tools. JEPSON, R. P. (1954). *Brit. J. industr. Med.*, **11**, 180. 18 refs.

An investigation was carried out at the Royal Infirmary, Manchester, to determine whether patients suffering from Raynaud's phenomenon as the result of using vibratory tools can be distinguished from normal subjects and from those in whom the condition is due to some other cause. The 34 patients examined were employed in a wide variety of occupations involving vibration. The onset of the condition followed a symptomless period of work with a pneumatic tool which ranged from one month to 20 years. Not all exposed workers developed Raynaud's phenomenon, but some, such as flangers and clinchers in the motor industry and shoe pounders, were particularly liable, symptoms often being noted within the first year. The fingers first affected were those most exposed to vibration. The symptoms appeared to reach a peak in their severity; thereafter they did not progress but persisted unchanged, even if the patient left the industry concerned. *X*-ray examination revealed carpal or metacarpal cysts in only four of the 34 patients. In all the patients there was a normal reaction to the hyperaemia test; fourteen developed white "dead" fingers when the hands were immersed in a water bath at 15° C. for 15 minutes. The response to the heat-flow test, carried out with a copper-tellurium heat-flow disk, was normal in thirteen out of 24 of the patients, compared with eight out of 29 healthy controls.

The author concludes that the diagnosis of Raynaud's phenomenon caused by vibratory tools must at present be made on clinical grounds. *John Pemberton.*

Robert Burns and his Heart. VINCENT, E. H. (1954). *Surg. Gynec. Obstet.*, **99**, 245. 5 refs.

Robert Burns, the eldest of the seven children of William Burnes [*sic*] and his wife, Agnes Broun, was born in January, 1759. Throughout his later childhood and adolescence the family went through difficult economic times; young Robert was assisting at the threshing when 13, and at 15 he was the principal labourer on the small family farm. During this period of overworked adolescence he suffered from numerous bouts of nervous depression, nocturnal headaches, and cardiac palpitation associated with feelings of faintness and suffocation. From this early strain he never really recovered, and in later life was seldom free from illness.

In 1784 Burns had a severe physical breakdown with alarming symptoms, and for this his physician, Dr. John Mackenzie of Mauchline, actually prescribed cold baths and continued farm work. During his visits to Edinburgh later on he had numerous riding accidents, and once was thrown from a coach and sustained a severely strained knee which laid him up for several weeks. This joint injury never healed satisfactorily in spite of the devoted ministrations of the celebrated Drs. James Gregory and Alexander ("Lang Sandy") Wood of Edinburgh.

Leaving the capital, where he realized his dazzling popularity would not last, Burns, in 1788, married Jean Armour and rented a small farm near Dumfries. At the same time he applied for a post with the Excise, hoping to combine the activities of farmer and exciseman. In spite of hard work the farm proved a failure, and in 1791, after ridding himself of the lease, Burns moved with his wife and family into Dumfries, where as exciseman his salary enabled them to live in some comfort. He did not regard himself as an invalid, but as a result of his frequent feverish illnesses and numerous accidents his activities were limited and he rested a great deal. In 1795 he was seriously ill with an arthritis and fever which his physicians called "flying gout". For this he was recommended sea-bathing and country life, and so poor Burns betook himself to Brow on the Solway. Writing from there to a friend, he describes himself as "pale, emaciated and so feeble as occasionally to need help from my chair—my spirits fled!" Returning shortly afterwards to Dumfries all the worse for his sea-bathing, he felt himself so near death that he wrote to his father-in-law asking Mrs. Armour to come immediately to look after Jean, who was expecting another child. Three days later, on July 21, 1796, Burns was dead.

The author of this article considers that there is no evidence to support the assertion of Dr. Currie, the poet's first biographer, that Burns died from alcoholic excess and venereal disease; rather is the evidence in favour of the diagnosis of rheumatic endocarditis as suggested by the late Sir James Crichton-Browne and others.

H. P. Tait.

Rheumatological Application of Radioactive Isotopes and of Radioactive Colloidal Gold in Particular. (Considérations rhumatologiques à propos des radio-isotopes et de l'or colloïdal radio-actif en particulier.) VERHAEGHE, A., and LEBEURRE, R. (1954). *Rev. Rhum.*, **21**, 120. 3 figs, 5 refs.

The authors report a preliminary study of the mode of action of gold therapy in chronic articular rheumatism using a preparation containing radioactive gold (^{198}Au). It was found that whereas radioactive iodine (^{131}I) injected into an arthritic joint in three cases had disappeared completely within an hour, ^{198}Au injected intra-articularly could still be detected up to 10 days later. In a fourth case ^{198}Au was injected intramuscularly and was found to accumulate steadily in an arthritic knee-joint, little or none being found in the opposite knee, for at least 5 days after injection.

No definite conclusions can be drawn from such small numbers, but the authors suggest that further systematic work on these lines might increase our knowledge of the role of gold salts in rheumatic therapy.

W. S. C. Copeman.

Three Cases of Lumbar Pott's Disease treated by Direct Approach. (Trois maux de Pott lombaires traités par abord direct du foyer.) DEBEYRE, J., SÈZE, S. DE, and MOREAU, C. (1954). *Rev. Rhum.*, **21**, 645. 4 figs.

Rheumatic Diseases, Rehabilitation, and the General Practitioner. KLEIN, R. (1954). *G.P.*, **10**, 49. 1 fig.